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DISORDERS OF SEXUAL DEVELOPMENT;
A CRYPTIC COMBO OF CARE

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ABSTRACT… Objectives: To evaluate the etiology, clinical presentations, investigations and surgical management of patients presenting with atypical genitalia in Pediatric surgery department. Disorders of Sexual development are one of the most complex congenital disorders encountered by the treating physicians. In recent years, the diagnostic ability and surgical techniques of gender reconstructions have improved remarkably. The spectrum includes chromosomal, genotype and phenotype abnormalities. The birth of a baby with atypical genitalia poses diagnostic and treatment challenges. This article focuses on etiology, clinical presentations, investigations and surgical management of patients presenting with ambiguous genitalia. **Study Design:** A descriptive, prospective case series. **Setting:** Department of Pediatric Surgery, Military Hospital, Rawalpindi, Pakistan. **Period:** October 2010 to June 2014. **Methods:** All patients with atypical genitalia, who underwent any kind of genital reconstruction surgery were included in the study. **Results:** A total of 28 patients were operated upon during the study period. Age ranged from 11months to 12 years. Patients were divided into two groups on the basis of their karyotyping. Seventeen patients had 46 XY and 11 had 46 XX. No mosaic pattern was seen. Male genital reconstructive surgery was done in 16 patients while 12 underwent female genital reconstructive surgery. **Conclusions:** Disorders of sexual development present as a complex spectrum of psychosocial, sexual, endocrine and surgical implications, thus management demands a multidisciplinary team approach. Appropriately timed surgical intervention after thorough work up and detailed counseling, produce excellent cosmetic and functional results.

Key words: Disorders of sexual development (DSD), Ambiguous Genitalia, Congenital Adrenal Hyperplasia (CAH), Intersex, Gender Assignment Surgery.

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INTRODUCTION

The birth of a child with disorder of sexual developement is not only distressing for the family but for the treating physicians as well. It's a psychosocial emergency especially in our culture, possibly due to taboos attached with such children.[1] Disparity between external and internal genitalia is usually obvious clinically. Gender assignment is a challenging task for the family and medical team. Shortly after birth, Pediatric endocrinologist excludes the salt losing congenital adrenal hyperplasia and starts hormones to correct the hormonal imbalance.[2]

Despite many controversies, surgery is required not only for the correction of appearance of the external genitalia but also for preservation of reproductive functions in future in addition to the psychosocial wellbeing of the individual.[3]

The aim of this study was to evaluate the etiology, clinical presentations, investigations and surgical management of patients presenting with atypical genitalia in Pediatric surgery department.

PATIENTS AND METHODS

A prospective study was conducted at the Department of Pediatric Surgery, Military Hospital, Rawalpindi, Pakistan, from October 2010 to June 2014. Data was collected and variables like age, clinical assessment and diagnostic modalities used, etiological factors, surgical procedure performed and complications were recorded. Analysis of all the cases managed during the study period was performed. Descriptive statistics were used to analyze the results. Outcome was assessed in terms of appearance of external genitalia and acceptance of assigned gender by parents and child if old enough to comprehend the issue.

RESULTS

A total of 28 patients were managed surgically for gender assignment. Age at the time of surgery ranged from 11months to 12 yrs. Patients were divided into two groups on the basis of their karyotyping. (In Group A, 17 patients with 46XY karyotyping and in Group B, 11 patients with karyotyping 46XX were enrolled). Nineteen out of 28 parents had consanguineous marriage. There was history of intake of antiabortion drugs used by mothers of 3 patients, history of unexplained neonatal deaths in the family and atypical external genital appearance in siblings was forthcoming in 5 and 7 cases respectively.

Ultrasound was done in all cases to assess the internal genitalia. Sinoscopy and laparoscopy were found to be the most helpful investigations in elucidating the exact anatomy of internal genitalia. After thorough clinical examination, karyotyping, hormonal assessment, ultrasound, sinoscopy and laparoscopy/ mini lap, gonadal biopsies (where needed) and extensive counseling of the parents, the decision of gender assignment was finalized and indicated surgeries were performed.

Group A contained 17 patients (60.7%) with karyotyping 46XY, the etiology was androgen insensitivity syndrome (AIS) in 12/17 (70.5%), mixed gonadal dysgenesis (MGD) in 4/17 (23.5%) and true hermaphrodite (TH) in 1/17 (5.8%) patients.

In group B, 11 patients (37.9%) with karyotyping 46XX were included, the etiology was congenital adrenal hyperplasia (CAH) in 10/11 patients (90.9%) and true hermaphrodite (TH) in 1/11 patient (9.0%). (Table-I).

A= 46XY N= 17		B= 46XX N=11	
AIS	12	CAH	10
MGD	4	TH	1
TH	1		

Table-I. Result

Male gender assignment surgeries were done in total 16 patients (57.1%), including 10 patients with partial androgen insensitivity syndrome (PAIS), 4 patients with MGD, 1 TH and 1 CAH. All 16 had undergone stage one surgery, nine out of them are completed with stage 2, and scortoplasty has also been done in 3 patients. Gonadectomies for streak gonads were done in 4 patients with MGD. Six orchiopexies were done. In 1 patient with CAH, who was reared as male, hysterectomy and oophorectomy was also done.

Female gender assignment surgeries were done in 12 patients (42.8%), including 9 patients with CAH, 2 patients with complete androgen insensitivity syndrome (CAIS) and 1 with TH. (Table-II). Two patients had isolated clitoral recession done, while 4 had undergone female genitoplasty with clitoral recession. Three patients had undergone orchidectomies for CAIS and TH.

Male= 16		Female= 12	
PAIS	10	CAH	9
MGD	4	CAIS	2
TH	1	TH	1
CAH	1		

Table-II. Reconstructive Surgeries

Enlarged clitoris with no testes palpable | Laparoscopy showed normal uterus | Normal looking ovaries on laparoscopy

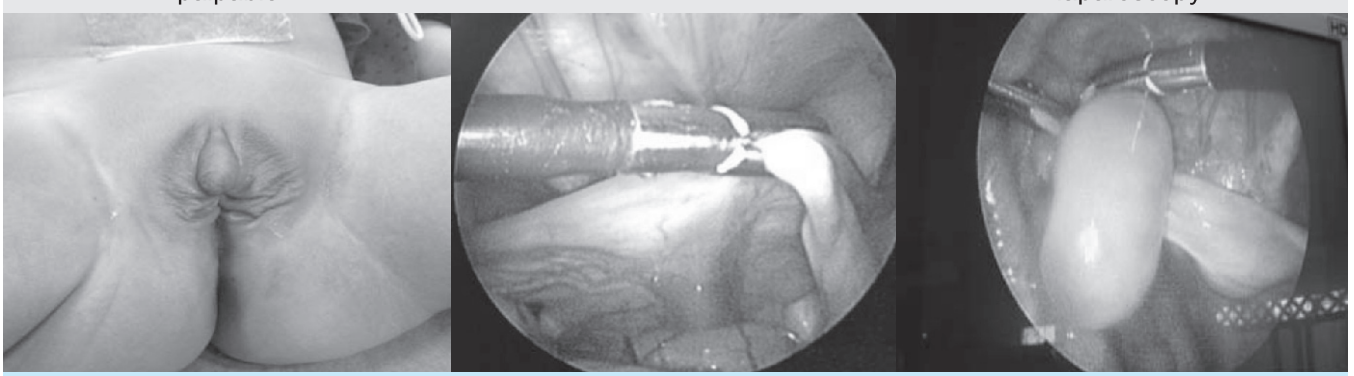

Fig-1. A patient of CAH , 46XX

A 3 yrs old baby presented with left inguinal hernia, almost no clitoral tissue visible

Ultrasound report of the with 46XY, labeled as CAIS

Hernial sac was containing gonad

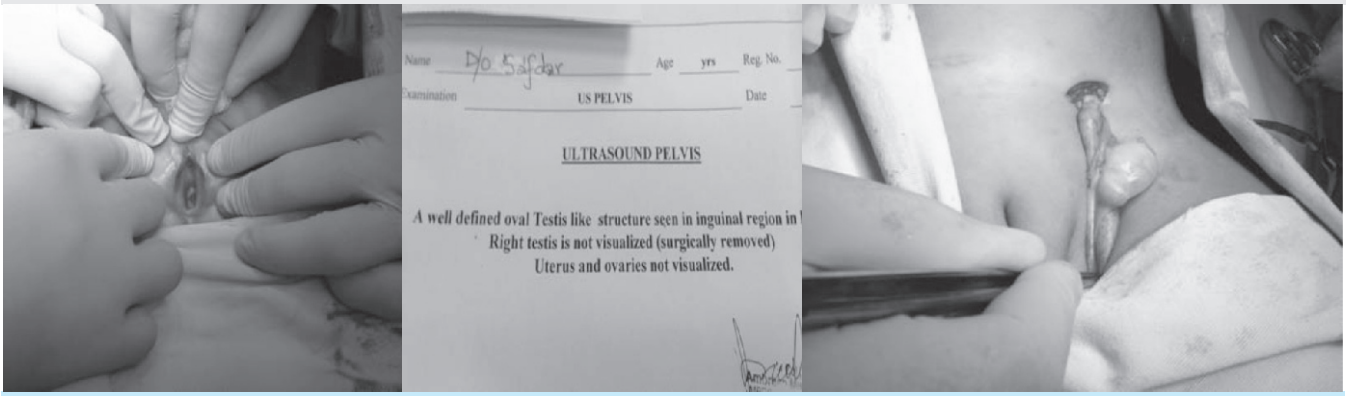

Fig-2. A 46 XY baby with female phenotype (CAIS)

A 2 yrs old boy having normal looking phallus with right testis in inguinal canal and left testis was not palpable

Mini lap showed streak left gonad with normal looking right gonad

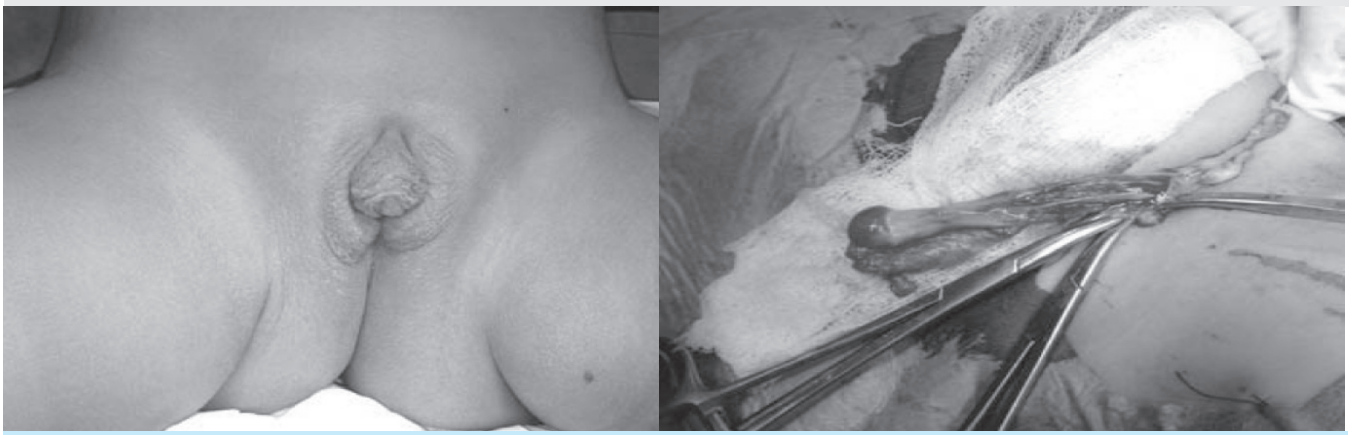

Fig-3. A 46 XY with Normal looking phallus (MGD)

TH, adequate phallus size with urogenital sinus

Laproscopy showing normal testis on one side and ovo testis on other side

Sinoscopy showed low confluenced urogenital sinus

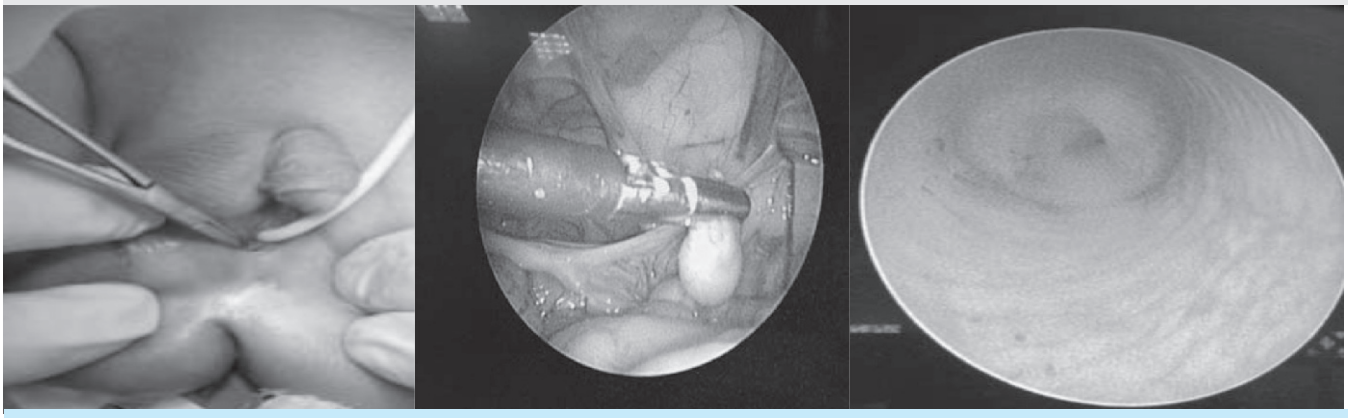

Fig-4. A true hermaphrodite with 46 XY

A 46 XX with enlarged clitoris | Immediate after surgery

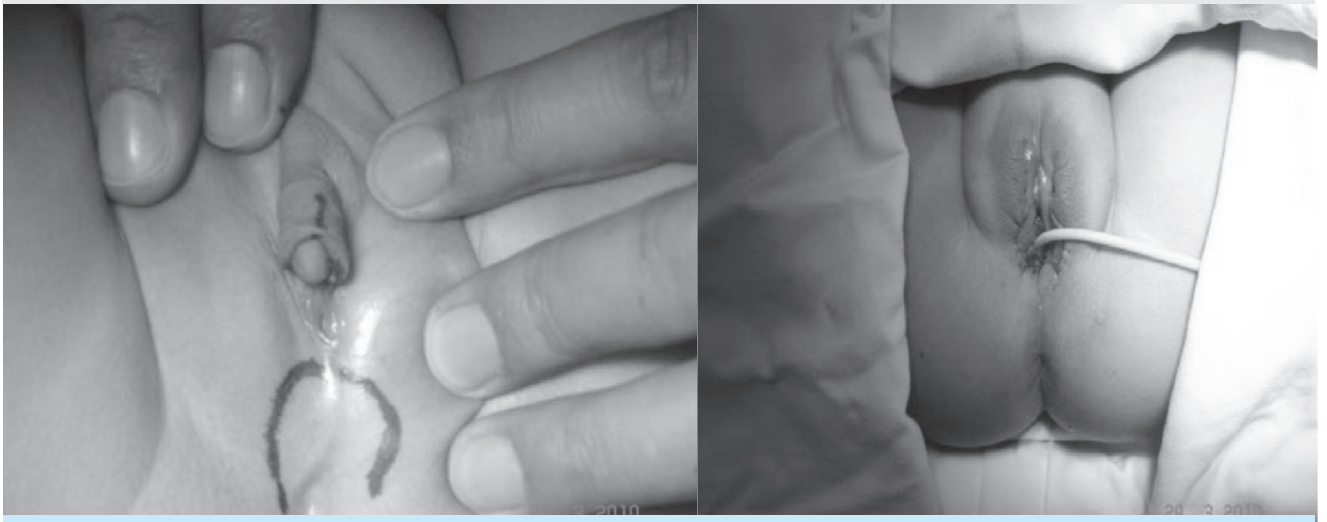

Fig-5. Feminizing genitoplasty for CAH

DISCUSSIONS

On the birth of a baby with atypical appearance of genitalia, extremely anxious parents want sex of their baby to be announced as early as possible. The role of neonatal endocrinologist is pivotal in stabilizing the patient, if any medical emergency in case of congenital adrenal hyperplasia exists. Subsequently the surgical team is involved to disambiguate the situation with help of clinical examination, followed by investigations and gender assignment surgeries, when and wherever required. The timings of investigations and surgery are debatable.[3,4] If gender re_ assignment is done in later age group, these children may find difficulty in adjusting themselves with peers, especially in society like ours where stigmatization of these children is a norm.[5]

A multidisciplinary team approach is mandatory for the management of DSD.[4] In our set up, most of the time, it's the pediatric surgeon who has to take lead in the group of treating physicians. Apart from clinical examination, karyotyping and ultrasound of abdomen, laparoscopy was found to be extremely useful in delineating the anatomy of internal gonads which ultimately helped in gender assignment, as advocated in literature[4,6] Once gender is assigned, early surgery was preferred on immense pressure of dysphoric parents probably because of the cultural environment where rearing such a child in a family privacy is a big issue and engendering differences face pear teasing at schools.[5]

In our series, no mosaic pattern was received, though cases are reported in literature.[7,8]

A complete assessment of DSD may require specialized investigations at genetic and molecular level which was not possible at our set up due to limitation of resources. Androgen gene receptor mutation, androgen binding activity of genital skin fibroblasts, 5 alpha reductase levels, Mullarian Inhibiting substance (MIS) and inhibin levels are not available, so diagnosis was possible with available resources only.

Ten undervirilized males were given trial of exogenous testosterone.[9,10] All of them were favorable penile responders and were considered to be the candidate for male gender reconstruction surgeries. When there was no clitoral tissue visible while child was standing, two of such patients were reared as female labeling the diagnosis of CAIS. Timing of orchidectomy in CAIS is controversial. Early gonadectomy is recommended because of fear of malignancy, while some advocate late removal of testes because of the fact that

aromatization of testicular androgens leads to estrogen production at puberty.[11] Another argument in support of this view is that, there is low risk of malignancy before puberty and testosterone may enhance breast development and bone mineralization. In both of our patients with CAIS who presented with inguinal hernia with palpable gonads, gonadectomy was done just after diagnosis and counseling of parents.

Pre surgical testosterone to enhance phallus size was used in 12 of the patients undergoing male genital reconstruction. These included 10 cases of PAIS, and one each of MGD and TH. Complications were encountered in 40% of these and mostly included urethral fistula and wound dehiscence.

Four patients with Karyotyping 46XY were labeled as partial MGD on clinical examination and operative findings. In all 4 patients, unilateral streak gonad was found at the time of orchipexy in asymmetrical patients when other testis was apparently normal and phallus was of good size. Gonadectomy was done in all 4 patients for the known risk of malignancy.[12] They were reared as male after counseling of parents. Mullarian structure was not excised, which was found in 2 patients on laparoscopy. On contrary, in international literature where female gender assignment is preferred in MGD however male gender assignment is recommended in cases of sever virilisation.[12,13] In such cases, gonads excision to prevent tumor developement is recommended followed by hormonal replacement therapy. If normal looking gonad is left, periodical biopsy of testis is recommended.[14]

One patient with 46XY and one patient with 46XX were labeled as true hermaphrodite when there was discrepancy between genotype and phenotype. Both had equivocal male and female external and internal genital organs on clinical examination. On laparoscopy, gonadal distribution was found lateral (a testis and a contra lateral ovary on histopathology) in both cases, justified them labeled as TH.[15] The gender assignment is governed by the size of phallus because these children are considered gender neutral at birth.[15,16]

Out of 10 patient of CAH with karyotyping 46XX, 9 had under gone female genital reconstruction. The timing of this surgery is controversial.[17] All of our patients were over 4 years of age except one, in which clitoral recession was done at the age of 1 year, to alleviate the immense anxiety of parents. In all of our patients, low type urogenital sinus was encountered and repaired without complications, however high type urogenital sinus is also reported in literature for which total urogenital sinus mobilization or vaginal replacement may be required.[1,18,19] (Fig-5).

The one remaining patient with CAH was a 12-year old who refused to be reared as female as he was the only “male” sibling in family. “His” 2 younger siblings also had CAH and were operated for feminizing genitoplasty. After counseling and considering their social issues, 2 staged male gender reconstruction surgeries were done. Residual urethral fistula is yet to be operated.

Peter A Lee et al have reported favorable outcomes, both social and sexual, in 46XY CAH cases, assigned male gender in a supportive cultural and social environment[20]. Shilpa Sharma from New Delhi also advocates that such children who present late should be involved in their gender reassignment discussion and should be allowed to make their own choice as they can have satisfactory life as adult male in the society[21].

It was observed, in our society male gender assignment is readily accepted and the parental anxiety is alleviated after first stage surgery despite of the complications associated with staged reconstruction of the severe hypospadiac deformity and the need for hormonal treatment. This utterance is strengthening the observation given in the previous study from the region in 2011.[5]

CONCLUSIONS

- Dealing with DSD, a coordinated team approach is required, which in our set up is

not always possible and pediatric surgeon has to take lead in discussions and decision making with parents.

- Though surgery is often cosmetic and may be damaging at times, but early surgery may be necessary to alleviate the anxiety of family; it's very difficult to delay the decision of surgery till puberty due to fear of peer teasing.
- Many diagnostic tools are not available to diagnose the genetic de-arrangements at molecular level; gender assignment should only be done with intense and continuous counseling and involvements of parents.
- Treating physicians should be very careful in choosing his/her words, repeated examination and photography
- There is no right course of action, long term goals have to be met with flexibility in the plans.
- For long term outcomes, prolonged follow up and multidisciplinary team management is needed at regional or national level.

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"We know what we are,
but know not what we may be."

William Shakespeare

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Dr. Naima Rasool	Perception, data collection, menu script writing and reviewed	