Management of ambiguous genitalia in ile ife, Nigeria: Challenges and outcome

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ABSTRACT

Background: Ambiguous genitalia are a major cause of parental anxiety and can create social problems if not properly managed. Diagnosis and management can however be challenging. The aim of this study is to highlight some of the challenges in management of ambiguous genitalia in our environment. **Patients and Methods:** All cases of ambiguous genitalia managed at the Paediatric surgical unit of the Obafemi Awolowo University Teaching hospital, Ile Ife, Nigeria, between January 1993 and October 2007 were analysed for age, sex at presentation, investigation modality, and final sex of rearing and outcome of surgery. **Result:** Nine patients had surgical reconstruction for ambiguous genitalia during the study period. Their age ranges from 5 weeks to 19 years at presentation. The causes of genital ambiguity in the patients was congenital adrenal hyperplasia (CAH) in 6, true hermaphroditism in 2 and male pseudo-hermaphroditism in 1. Seven patients were reconstructed as females while 2 were raised as males. Change of sex of raring was necessary in 2 patients. **Conclusion:** The diagnosis and management of ambiguous genitalia is a challenging problem in our environment. Early presentation and treatment is necessary to avoid psychological and social embarrassment.

Key words: Ambiguous genitalia, children, treatment

INTRODUCTION

The first question that usually arises after the birth of any newborn is about the gender of the child. This is easily answered in most cases by simple examination of the external genitalia of the baby. Genitalia are ambiguous whenever there is difficulty in attributing gender to a child based on the appearance of the external genitalia.[1,2] The appearance of the external genitalia is a result of complex interaction between genetic and endocrine processes during fetal development. Abnormalities of the external genitalia sufficient to warrant genetic and endocrine studies is said to occur in 1 in 4,500-10,000 births.[3,4] Ambiguous genitalia are a major cause of parental anxiety and can create psychological and social problems if not properly managed. Also life threatening conditions such as salt wasting crisis of congenital adrenal hyperplasia (CAH) need to be detected and treated early.[5] Diagnosis and management of this condition can be challenging requiring a multidisciplinary approach.[6]

There has been considerable progress in diagnosis and management in recent decades especially in CAH.[3] This is the commonest cause of ambiguous genitalia of the newborn and can now be suspected and treated from *in utero*.

There is presently a paucity of information on the challenges and outcome of management of ambiguous genitalia in our environment. The aim of this study is to document and highlight the challenges in diagnosis and management of ambiguous genitalia in a cohort of Nigerian children seen at a teaching hospital in South Western Nigeria.

PATIENTS AND METHODS

This is an analysis of cases of ambiguous genitalia managed at the Obafemi Awolowo University Teaching hospital, Ile Ife, Nigeria between January 1993 and October 2007. The patients were analysed for age, sex at presentation, investigation modality, and final sex of rearing and outcome of surgery. Barr body evaluation, sonogram, mini-laparotomy and cystoscopy were the main methods of evaluation while hormonal assay was requested if patient can afford it. Surgical reconstruction is embarked upon after dialogues with parents especially in cases requiring change of sex of raring [Figures 1 and 2].

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Figure 1: 18 month-old child with true hermaphroditism

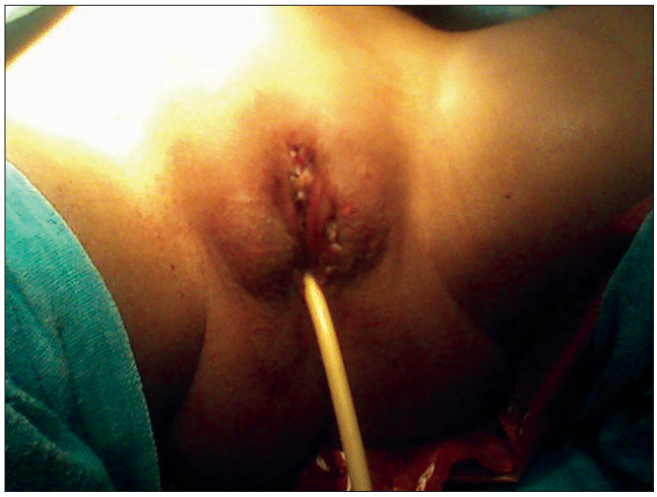


Figure 2: Same child in figure 1 after surgical reconstruction

RESULT

Ten patients were seen with ambiguous genitalia during the study period but only 9 patients had surgical reconstruction for ambiguous genitalia. The median age at presentation was 3 years. None of the patient presented in the neonatal period. The earliest presentation was 5 weeks while the oldest was 19 years. Presenting features were abnormal looking genitalia since birth in 7 patients. Clitorimegaly was noticed at 2 and ½ years and 3 years in 2 patients who are siblings and whose mother had been on fertility drugs prior to their conception. There were 2 patients who are a set of twins. The oldest patient in this series had gynaecomastia noticed since puberty.

All patients had routine haematological investigations done which were normal. None of the patients had karyotyping done because it was not available; however, Barr body examination was positive in three patients who ultimately turned out to be female. Most of the patients were not able to afford biochemical hormonal assay but 2 patients who had the investigation was inconclusive although the patients were thought to have congenital adrenal hyperplasia. Diagnosis was based mainly on demonstration of the internal genitalia. Ultrasound was done in 8 patients but the findings correlated with laparotomy findings in only three while in 2, the presence of uterus and adnexiae was suggested but was absent at laparotomy. In the other 3 patients the preliminary ultrasound was inconclusive. In all, seven patients ultimately required laparotomy and another one laparoscopy to define the internal genitalia [Table 1]. Two of the patients had suspicious gonads on laparotomy and these were biopsied. Their histology confirmed ovotestis. The gonadal biopsy result changed the diagnosis from CAH in one of the patient to true hermaphroditism.

The final diagnosis of the causes of genital ambiguity in the patients was CAH in 6, true hermaphroditism in 2 and male pseudo-hermaphroditism in 1. Seven patients were reconstructed as females while 2 were raised as males. Change of sex of raring was necessary in 2 patients. These two patients had change of name while one of the parents had to relocate.

DISCUSSION

Children born with the intersex problem comprise about 1.7% of all live births.[7] The incidence of this condition in the African population is unknown.

Ambiguity of the external genitalia is easily recognised at birth and the apparent sex of rearing will be obvious.[8] The general consensus is that the diagnosis should be promptly established preferably before discharge so that an early sex of raring can be assigned to the child as well as to plan treatment.[1,2] This aspect of the patient's management is important to facilitate psychological development and good quality of life in the affected individuals. Assigning a sex of raring to the child requires that elaborate investigation be done to ascertain the genetic or endocrine causes of the anomaly. This early part of the child's management should ideally be a multidisciplinary approach. In many institutions in developed world, there are joint clinics established for the management of these patients where collective decisions are made concerning each patient.[6,9] This type of clinic is not present in our own part of the world therefore each patient does not have that benefit.

Investigating a child with ambiguous genitalia requires both genetic and hormonal studies to establish the diagnosis and plan appropriate treatment. A fast buccal

Table 1: The clinical presentation, investigation and management outcome of patients with ambiguous genitalia

Age at presentation	Presenting complaints	Physical examination	Biochemical investigations	Radiological findings	Cystoscopy	Laparotomy /laparoscopy findings	Karyotype	Final diagnosis	Definitive surgery done	Age at surgery	Outcome	Secondary surgery?	Duration of follow up
9 years	Ambiguous genitalia	Clitorimegaly, cordee, fused labioscrotal folds. Blind ending vagina	Hormonal assay not done	USS- rudimentary ovaries and broad ligament Sinogram- not conclusive	Not done	Normal ovaries, uterus and fallopian tubes	Not available	CAH	Clitoral resection + vaginoplasty	9 years	Vaginal stenosis	Serial dilatation + repeat vaginoplasty at 1 and 3 years after primary surgery	16 years
3 years	Abnormal looking genitalia since birth	Clitorimegaly, hypoplastic labial folds, blind ending vagina	Not done	Conflicting	Not do ne	Normal ovaries, uterus and fallopian tubes	Not available	CAH	Clitoral resection + vulvo-vaginoplasty	3 years	Partial wound dehiscence Vaginal stenosis	Dilatation	7 years
5 weeks	Abnormal looking genitalia since birth	Clitorimegaly, single perineal opening. No palpable gonads	FSH 4miu/ml (Normal 1-14miu/ml) LH 0.08 miu/ml (Normal0.7-7.4miu/ml) Testosterone 0.09ng/ml (Normal 0.3-1.3ng/ml) and 17 ketosteroids 0.4mcg/ml (Normal 1.7-3.6mcg/ml)	USS- Equivocal	Common urogenital sinus with 2.5 cm between vagina and urethra	Normal ovaries, uterus and fallopian tubes		CAH	Clitoral resection + vulvo-vaginoplasty	18 months	Nil	Nil	4 years
5 weeks	Abnormal looking genitalia since birth	Clitorimegaly, single perineal opening. No palpable gonads	FSH 0.0238miu/ml (Normal 1-14miu/ml) LH 0.331 miu/ml (Normal0.7-7.4miu/ml) Testosterone 0.04ng/ml (Normal 0.3-1.3ng/ml) and DHEA 0.3ng/ml(1.7-3-.6ng/ml)	USS- Equivocal	Common urogenital Sinus with 2.5cm between vagina and urethra	Normal ovaries, uterus and fallopian tubes		CAH	Clitoral resection + Vulvo-vaginoplasty	18 months	Nil	Nil	4 years

Table 1: Contd...

3 years	Enlarged clitoris 6/12	Clitori-megaly 3 cm, partly fused labia, small vagina opening	Nil	Uterus, ovaries normal	Not done	Not done	Not available	CAH	Clitoral resection and V-Y plasty of fused labia	3 years	Satisfactory	Nil	2 years
5 years	Enlarged clitoris of 2 years	Clitori-megaly	Not done	Uterus, ovaries present	Not done	Not done	Not available	CAH	Clitoral resection and vulvo-vaginoplasty	5 years	Satisfactory	Nil	2 months
1 year	Enlarged phallus, fused labia, vagina not seen	Clitorimegaly, palpable R gonad	Not done	Uterus, ovaries present	Not done	Normal uterus, Lt ovary, R gonad had areas of testicular tissue. Gonadal biopsy confirmed testicular tissue	Not available	True hermaphrodite	Clitoral resection and vulvo-vaginoplasty + Rt Gonadectomy	18 months	Satisfactory	Nil	1 year
1 year	Abnormal looking genitalia	Hypospadic phallus with a single perineal opening. No Palpable gonad	Not done	Sonogram equivocal. Presence of ovaries and uterus on USS	Not done	Absent female internal genitalia. Both testis in the deep ring	Not available	Male Pseudohermaphroditism	Orchipexy follwed by delayed hypospadia repair	2 years	Satisfactory	Nil	1 year
19 years	Abnormal looking genitalia since birth. Gynaecomastia	Gynaecomastia. Hypospadic phallus Impalpable left gonad	Not done	USS suggest presence of tubes and ovaries	Not done	Presence of left fallopian tube, Abnormal looking left gonad which on histology an ovotestis	Not available	True hermaphrodite	Left gonadectomy Bilateral mastectomy Hypospadia repair	19 years	Satisfactory	Nil	4 months

*Required change of sex of raring, USS = Ultrasound, CAH = Congenital adrenal hyperplasia

smear for the presence of the extra X-chromosome will help in establishing a suspicion of the chromosomal constitution of the individual. This test has however been found to be unreliable and cannot be solely relied upon. Karyotyping an important early test using cultured leucocytes is not available in our hospitals and so cannot be used.

There are a myriad of hormonal assay that assist the clinician in establishing diagnosis of ambiguous genitalia including serum testosterone, DHT, gonadotropins and adrenal steroids such as 17-hydroxyprogesterone,17-hydroxypregnenalone, androstenedione and dehydroepiandrosterone (DHEAS) and 11-hydroxycortisone, mullerian inhibiting substance (MIS). These hormonal assays are very expensive and can barely be afforded by the patients. Only 2 of our patients had enough money to go for hormonal assay but the results were not helpful in the twins who are suspected to have adrenogenital syndrome. Specific assay for enzymes such as 5 alpha reductase, 21-hydroxylase are available in developed countries. All these are not available in Nigeria.

In our environment, the incidence of these anomalies is unknown. It is obvious that the cases of suspected CAH that we see in our setting are the non salt wasting type as most of these ones may have succumbed at birth or in the perinatal period. Nowadays cases of CAH are diagnosed *in utero* especially if there is a previous or family history of the disease. Chorionic villous sampling during the first trimester or amniotic fluid sampling will help to establish the diagnosis. These patients are given dexamethasone *in utero* before the period of sexual differentiation thereby reducing the chance of genital ambiguity. Two of the patients we have managed are siblings and there is the possibility that there is a genetic disorder in these patients although there was also a positive history of maternal ingestion of fertility drugs which may be progestogens during pregnancy with these children. It is also interesting that two of the patients are also twins in which case a genetic predisposition or enzyme deficiency was very likely. There are no facilities to determine the specific enzyme deficiency in these patients.

In our setting, late presentation seems to be the case as only one of the patient presented early. Late presentation can lead to a myriad of problem in the subsequent management of these patients as wrong assignment of sex can lead to serious consequences in the future. Even where correct sex of rearing has been done, long-term psychopathologic disorders including gender identity disorder and deviant gender role may develop.[10] Two of our patients require that the sex of raring be changed because the final diagnosis dictated that the appropriate genital reconstruction be done. A similar case of sex conversion in a 21 year old patient has been reported from the eastern part of Nigeria.[11] In general, the assignment of sex for rearing must be guided by the etiology of the genital malformation, the anatomic condition, and family considerations.[6] Recognition of parental acceptance is a fundamental determinant of success of any management strategy in the case of intersex children is critical.[8]

In conclusion, the management of a child with ambiguous genitalia is a challenging problem in our environment. Early presentation and treatment is necessary to avoid psychological and social embarrassment. The ability to do this is limited in most resource limited areas. Continue reliance on history, physical examination, and limited investigative facilities available will continue to be the only reliable mean of diagnosis and management.

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