

Ambiguous External Genitalia in Childhood in Port Harcourt, Nigeria

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Abstract

Ambiguous external genitalia are a major cause of parental anxiety and a challenge to paediatricians in developing countries.

Aims and objectives: This study aims to highlight the pattern of presentation and challenges in the management of ambiguous external genitalia in a developing country.

Patients and methods: A prospective study of all patients with ambiguous external genitalia managed in the paediatric endocrine unit of the University of Port Harcourt Teaching Hospital between January 2008 and Dec 2010 was done. Biodata, clinical presentation, management and outcome were documented.

Results: Six patients were seen with ambiguous external genitalia during the study period. Age ranged from birth to 16 years at presentation. The commonest presentation was clitoral hypertrophy in all patients. The commonest initial diagnosis was CAH.

Definitive confirmation of cause of ambiguous external genitalia with a reconstructive surgery was done in only one patient due to non-availability and high cost of investigation. Three (50%) patients were lost to follow up of which 2(66.7%) have resorted to spiritual treatment. One patient who presented at 16 years of age died from an associated obstructive uropathy with chronic renal failure.

Conclusion: The challenges in managing children with ambiguous external genitalia in developing countries include late presentation, high cost and non-availability of investigations for making definitive diagnosis.

Keywords: Ambiguous; External genitalia; Childhood; Port Harcourt

Introduction

The external genitalia are considered ambiguous whenever there is difficulty in assigning gender to a child based on the appearance of the external genitalia [1,2]. It is a common presentation of children with disorders of sex development (DSD) and a cause of parental anxiety. Abnormalities of external genitalia occur in 1.7% of new born in developed countries [3]. In most developing countries, the prevalence is unknown; however reports of cases are on the increase. Globally, approximately 1 in 2000 children is born with DSD [4].

The appearance of the external genitalia is a complex interaction between genetic and endocrine processes during fetal development [5]. There are various causes of ambiguous genitalia; it can either result from over-virilisation or masculinization of 46, XX female from androgen excess, or under-virilisation or under-masculinization of 46 XY male due to a disorder in androgen synthesis or action. AEG is classified into gonadal dysgenesis, male or female pseudo hermaphroditism now referred to as 46XX and 46XY DSD or true hermaphroditism now Ovotesticular DSD [6]. The latter is rare, seen in about 10% of cases of ambiguous genitalia [7]. In Ovotesticular DSD there is an asymmetrical gonadal development or presence of ovary and testis.

The commonest reported cause of ambiguous external genitalia from studies is congenital adrenal hyperplasia (CAH) due to deficiency in enzymes needed in cortisol biosynthesis leading to excess of androgens [8,9]. The birth of a child with ambiguous genitalia still represents an enormous challenge especially in developing countries with limited diagnostic and therapeutic facilities, for this reason, the structuring of diagnostic procedures, decision making and therapeutic

interventions for a child with ambiguous genitalia should involve a highly specialised team of physicians of different subspecialties. An expert to give psychosocial care is also needed to counsel parents and patients accordingly.

There has been considerable progress in the diagnosis and management of cases of ambiguous genitalia especially in CAH [10]. This is because CAH is the commonest cause of ambiguous genitalia of the new born and can now be suspected and treated *in utero* [10]. Although the lesions are benign, early detection is important so as to assign the correct gender at birth and prevent avoidable complications which may occur later in life. Early treatment in most cases of ambiguous external genitalia is associated with little or no sequelae [11].

In resource poor regions, late detection due to poor awareness, limited diagnostic ability and facilities have formed a major constraint to identifying and treating children with various forms of DSD [12].

This report highlights the challenges in diagnosis and management of ambiguous genitalia in cases seen at a tertiary centre in Southern Nigeria.

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Subjects and Methods

This was a prospective review of all patients with ambiguous external genitalia seen at the endocrine unit of the department of Paediatrics; University of Port Harcourt Teaching Hospital from January 2008 to December 2010.

The paediatric endocrine unit of the University of Port Harcourt Teaching Hospital was established in 2002 and has since been functional. The hospital is a teaching and research centre in the southern part of Nigeria. It serves as a primary and referral centre to other hospitals in Rivers State and neighbouring states such as Abia, Imo, Bayelsa, Akwalbom states. The hospital serves a population of over 1 million children in Rivers State and neighbouring states. All children with various endocrine conditions are referred to the paediatric endocrine unit. The evaluation of the children include detailed history, physical examination, place of birth, age and sex of rearing at presentation, clinical presentation, investigations, management and outcome of treatment /follow up. Routine investigations request for all children with ambiguous external genitalia were Barr body evaluation, Karyotype, Abdominopelvic ultrasounds scan, serum electrolyte and hormonal assay. The diagnosis of ambiguous external genitalia was made based on inability to determine the sex of the child on physical examination. Patients are usually co-managed by paediatric surgeons, psychologist, pathologist and radiologist.

Results

There were six cases seen with varying degrees of genital ambiguity. The ages of the patients at presentation ranged between birth and 16 years. Two patients presented in the neonatal period. No patient had history of vomiting or collapse in the neonatal period. There were no other associated congenital anomalies in all patients. They are all products of non-consanguineous marriages.

Patient 1

This patient was delivered in a tertiary health facility and diagnosed at birth with ambiguous looking external genitalia; this was characterized by hypertrophy of the clitoris, fused labia and a perineal orifice. Serial serum electrolyte, urea and creatinine (S/E/U/Cr) and blood glucose were normal. Abdominopelvic ultrasound scan (USS) showed female gonads which was confirmed by a minilaparotomy. Karyotype done at 2 years of age was female. Hormonal assay confirmed a congenital adrenal hyperplasia (CAH). Sex of rearing was female. Reconstructive surgery was done outside the country at 2 years. She is on follow up.

Patient 2

This is an eight day old baby referred by a nurse for short penile length at circumcision. On examination there was hypertrophy of the clitoris, non-palpable gonads and urethral opening could not be appreciated. Buccal smear was positive for Barr body, serial S/E/U/Cr and blood glucose were normal, in Abdominopelvic USS /Magnetic resonance imaging ovarian or testicular tissues were not appreciated. Karyotype and hormonal screen could not be done. Parents objected to minilaparotomy. Sex of rearing was male, no treatment was commenced and patient was lost to follow up.

Patient 3

5 weeks old who presented with ambiguous external genitalia from birth. Patient was delivered in a private clinic. On examination

of external genitalia there was hypertrophy of the clitoris, rudimentary scrotal sac, and perineal orifice with no palpable gonads. Patient presented for persistent vomiting. S/E/U/Cr showed hypernatremia and hyperkalaemia with increased urea. Ovaries or testicular tissues could not be visualized on Abdominopelvic USS. Karyotype and hormonal screen could not be done. Patient is awaiting minilaparotomy. Has been commenced empirically on steroids.

Patient 4

This is a 7 months old who presented on account of abnormal looking external genitalia characterized by hypertrophy of clitoris, rudimentary scrotal sac with no palpable gonads and no visible urethral orifice. At Abdominopelvic USS, ovaries or testicular tissues could not be visualized, S/E/U/Cr were normal, Karyotype and hormonal screen could not be done. Sex of rearing was male. Patient was lost to follow-up and parents believe child's problem is spiritual.

Patient 5

This 7 year old presented with complaint of progressive swelling in the vagina. Examination of the external genitalia revealed hypertrophy of the clitoris with a urethral opening at the tip. There were no gonads felt, vaginal opening was present. Abdominopelvic ultrasound scan to detect the gonads was not conclusive. Karyotype and hormonal screen were not done. The sex of rearing was female. She was also lost to follow up. Parents also believe child's problem is spiritual.

Patient 6

This is a 16 year old who presented with ambiguous external genitalia from birth, difficulty in micturition from birth which worsened a week prior to presentation, vomiting of one week and recurrent convulsion a day prior to presentation. Parents brought child because of the recurrent convulsion. She has been reared as a female despite the genital ambiguity. Examination revealed a small for age child, she was drowsy and pale with a PCV of 17% and severe hypertension. Examination of the external genitalia revealed hypertrophy of the clitoris, fusion of the labia with no palpable gonads. There was a common vaginal and urethral opening which was difficult to catheterize. She has achieved breast and pubic hair development at Tanner stage 2 and 3 respectively, no menarche. S/E/U/Cr revealed markedly raised urea and creatinine (14.3mmol/l and 1485umol/l respectively). Abdominopelvic ultrasound scan showed evidence of an obstructive uropathy with calyceal dilatation. Karyotype and hormonal screen could not be done. She died after four days on admission from chronic kidney disease before dialysis could be commenced.

Table 1 shows the summary of clinical profile and outcome of management of the patients.

Discussion

Ambiguity of the external genitalia is the commonest mode of presentation in children with DSD [13]. The birth of a child with ambiguous genitalia is a major cause of parental anxiety and can lead to psychosocial problems if not managed properly. The general consensus on the management of a child with ambiguous genitalia is for prompt diagnosis to be made before discharge so that an early sex of rearing can be assigned to the child as well as to plan treatment [2]. Only one of the cases in this report was detected at birth this may be because the child was born in a tertiary health care centre with specialist in attendance.

Age at presentation/ Place of Birth	Presenting Complaints	Features at presentation	Clinical diagnosis	Radiologic investigation	Investigations done	Laparotomy/surgery done	Treatment/outcome
(Patient 1) At birth/Teaching hospital	Abnormal looking external genitalia	Clitoral hypertrophy, fused labia, perineal orifice	Ambiguous genitalia 2° to CAH	Abdominopelvic USS ovaries and uterus visualized	Serial S/E/U/Cr normal, Serum glucose normal, Karyotype female, hormonal screen suggest CAH	Minilaparotomy reveals ovaries and uterus present.	Sex of rearing female / External genitalia reconstructed at 2years.
(Patient 2) 8days/Maternity home	Referred for short penile shaft noted at circumcision	Clitoral hypertrophy, absent urethral opening, gonads not palpable	Clitoral hypertrophy 2° CAH	No ovarian or testicular tissues appreciated on abdominopelvicScan and Magnetic resonance imaging	Buccal smear positive for bar body, S/E/U/Cr- Normal.	None	Nil/ sex of rearing male/ lost to follow-up
(Patient3) 5weeks/Private clinic	Ambiguous external genitalia at birth, persistent vomiting	Hypertrophied clitoris, rudimentary scrotum, orifice in perineum, no gonads palpable	Ambiguous genitalia 2° to CAH (Classical) Perineal hypospadias	Ovaries and testicular tissues could not be appreciated	Na+ 115mmol/l, K+ 6.0mmol/l, HCO2+ 14mmol/l, Urea 15.5mmol/l, Cr. 50umol/l,	Not yet	Steroids/ sex of rearing female/ Awaiting karyotype result/ Booked for minilaparotomy.
(Patient4) 7months/Private clinic	Abnormal genitalia from birth	Clitoral hypertrophy, rudimentary scrotal sac, no urethral opening, non- palpable gonads	Ambiguous genitalia 2° to CAH	Abdominopelvic ultrasound scan (ovaries and testicular tissue not visualize	S/E/U/Cr (Normal), hormonal screen not done	None	Nil/ sex of rearing male/ lost to follow up
(Patient 5) 7years/General hospital	Swelling in the vagina	Clitoral hypertrophy	Ambiguous genitalia 2° to CAH	Abdominopelvic ultrasound scans not conclusive.	S/E/U/Cr (Normal), CAH screen not done	None	Nil/sex of rearing female/ lost to follow-up
(Patient 6) 16years/Traditional birth attendant	16 years/ Traditional birth attendant	Ambiguous genitalia, difficulty in catheterization, Hypertension, Tanner stage 2&3 for breast and pubic hair development respectively.	CRF with ambiguous genitalia	Abdominopelvic scan revealed calyceal dilatation.	Creatinine (1485umol/l), Urea (14.3mmol/l), K+ (5.2mmol/l), HCO (11mmol/l), PCV 17%		Antihypertensive, antibiotics, Dialysis (not done)/sex of rearing female. Outcome –died

Table 1: Summary of Clinical Features of Children with ambiguous external genitalia.

The late presentation of most cases in this report is however similar to reports from other parts of Nigeria, [12,14,15] this goes to highlight the low level of awareness of this condition in our environment despite the fact that most of the children were born in hospitals. It could also be due to lack of careful examination of the external genitalia to detect subtle aberrations especially in the neonatal period. In most developing countries such as Nigeria there is poor level of awareness and many children with even major aberrations of external genitalia are missed at birth, this resulted in the challenges of gender reassignment [12,14,16].

The clinical presentation of genital ambiguity (GA) varies. However for uniformity, the diagnostic criteria proposed by Danish et al. [17] in 1982 are one of the most often cited in the literature and is easily applicable in medical practice. According to this classification, there is GA if any of the following characteristics are observed.

In genitalia apparently male in appearance absence of palpable gonads, stretched penile length below 2.5 standard deviations from the mean for age; small gonads, i.e. largest diameter smaller than 8 mm, presence of an inguinal mass (which could correspond to rudimentary uterus and Fallopian tubes) and hypospadias signifies ambiguity. In genitalia apparently female in appearance clitoral diameter greater than 6 mm, palpable gonad within labioscrotal fold, posterior labial fusion, an inguinal mass which could correspond to testicles signifies ambiguity. In this study as in most other studies, [9,14,15,18] the commonest presentations of ambiguous external genitalia are clitoral hypertrophy, significant micropenis, fusion of labioscrotal fold, hypospadias, absent

urethral opening and non-palpable gonads. In this study, all patients had clitoral hypertrophy. Clitoral hypertrophy was recorded in 92.9% and 77.2% of cases in a Saudi Arabian and Australian study respectively [9,18]. Clitoral hypertrophy is also the commonest finding in patients with 46XX DSD [9,15]. In the study done in Saudi Arabia amongst 40 neonates in 2009, 14 were genetic females out of which 13(92.9%) had clitoral hypertrophy. This is similar to finding done in Benin amongst females with ambiguous genitalia where the commonest reported finding was clitoral hypertrophy amongst 47.5% of the patients. On the other hand, micropenis, hypospadias and palpable gonads/ Undescended testis are common presentations in genetic males. The genetic sex of most of our patients were not determined to determine the presentations of the females and males, however this number was small to make a specific conclusion. Though none of our patients had a family history or associated gross extra genital malformations, these are possible findings [9]. In the Study in Saudi Arabia, [9] 11(26.8%) patients had extra genital malformation and there was a positive family history in 3 children.

The commonest clinical diagnosis was (CAH), only one patient had a clinical event suggesting a salt losing crisis, and this either suggests a rarity of the salt wasting form of CAH or non-detection of cases of salt losing forms that die. There was no history of ingestion of drugs by mothers that could be implicated in all patients reported.

The management of a child with ambiguous genitalia needs a multidisciplinary approach involving the paediatrician,

endocrinologist, surgeon, psychologist and if need be a religious leader [13]. In many institutions in developed world, there are joint clinics established for managing these patients. This is to enable quick and collective decisions to be made concerning each patient [9]. In our centre, there are no such clinics and patients are usually seen first in the paediatric endocrine clinic from where consults are sent to other units involved in the management of these patients, this could involve several appointments which can be a major reason for loss to follow up as was seen in this study. Elaborate investigations are required to ascertain the genetic or endocrine causes of the anomaly. Karyotyping is an important early test using cultured leucocytes to determine the actual genetic sex of the patient [13,14]. It describes the number of chromosomes, and what they look like under a light microscope. Attention is paid to their length, the position of the centromeres, banding pattern, any differences between the sex chromosomes, and any other physical characteristics. Karyotyping was done on only one patient, who did outside the country as it is not available in our centre necessitating the use of a Buccal smear. Buccal smear has however been found to be unreliable and cannot be solely relied upon as was noted in this study. Serial measurement of glucose and electrolytes may show hypoglycaemia and the classical hyponatraemia and hyperkalaemia when salt losing Congenital Adrenal Hyperplasia (CAH) is expected especially in the new born period. There are a lot of hormonal assays that can be done to assist the clinicians in establishing diagnosis; however the number can be reduced by considering the genetic sex of the patient, [13] with genetic females and suspicion of androgen excess, initial hormonal assay is limited to adrenal hormonal steroid precursors (17-hydroxyprogesterone, androstenedion and DHEA-S). Other hormones such as testosterone, gonadotropins, mullerian inhibitory substance can be done. These hormonal assays could not be done by most of our patients due to non-availability and cost; this is similar to report in Ile Ife Nigeria where most patients could not do the hormonal assays and when it was done it was not very useful as interpretation was difficult [14].

Laparoscopy/minilaparotomy in the evaluation of children with ambiguous external genitalia is very important especially in developing countries, [12,18] this is because there is usually a challenge in determining genetic Sex of the children especially in developing countries where Karyotyping and sophisticated imaging facilities are not available or require highly trained personnel. In our study, only two patients could do Barr body estimation which was unreliable in determining definitive sex. Pelvic ultrasound for visualisation of gonads was inconclusive in all but one patients reported on; this is also a common finding in other studies done in other developing countries. The poor yield from imaging could be due to poor technique and expertise and also ovaries are not readily identified on ultrasound during phase of low gonadotropin stimulation [13]. In view of this, many affected children required mini-laparotomy for direct visualization and biopsy of gonads, this approach to confirm or assign gender was adopted and found helpful by earlier authors in low resource regions [12,14,20]. The direct visualization of internal genitalia in other cases is also important to ascertain their normalcy for the purpose of sexual functions and reproduction [21, 22]. Though the acceptance of minilaparotomy by parents have posed a great problem which accounted for the low rate in this study, however in the study in Ile Ife, [14] in Western Nigeria laparotomy was the major tool of diagnosis and helped to determine sex of rearing and possibly determine the appropriate genital

reconstruction surgery. Only one patient who was seen at birth had a minilaparotomy, which revealed female genitalia and was confirmed by Karyotyping. She has had a reconstructive surgery.

The treatment of a child with ambiguous external genitalia requires a multidisciplinary approach and the team should be introduced to the parents at an early stage this is to aid early diagnosis and sex assignment and type and time of reconstructive surgery. Management of subsequent pregnancies should also be planned which include the possible use of prenatal diagnosis in suspected CAH and use of dexamethasone by the mothers in early pregnancy until the sex of the baby can be confirmed [13].

Most of our patients were lost to follow up, this is because investigations were either not available and or expensive and patients could not afford them. Also considering the importance of male children in our society, it was difficult for parents to accept the fact that there male babies could be females. This prompted most of the parents to feel their children's condition was spiritual and beyond medical science as was noted in this study where two patients contacted after loss to follow up stated that their child had a spiritual problem not medical and were not willing to return for further evaluation.

In conclusion, the management of a child with ambiguous genitalia is still a challenge in our environment. Poor awareness and beliefs, late presentation and lack of diagnostic facilities still remain a major challenge.

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