Ambiguous External Genitalia Presenting With Chronic Renal Failure In Port Harcourt

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Abstract

A 16-year old presented with ambiguous external genitalia (AEG) and difficulty in passing urine since birth. She developed vomiting, generalized convulsion and reduced urine output three days prior to presentation. This case highlights management challenges and a rare complication of a case of (AEG).The patient was small for age, restless, with a blood pressure of 170/100mmHg. Genital examination revealed clitoral hypertrophy, fusion of labia majora and minora with no urethral opening. There was no palpable gonad in the inguinal region. Pubic and axillary hair development was at Tanner stage II and III respectively. Investigations revealed anaemia, renal failure with a Glomerular Filtration rate of 4.72ml/min/1.73m^2. Abdominal ultrasound scan showed echogenicity and poor corticomedullary differentiation of both kidneys with obstructive changes marked on the right. She has had no previous evaluation for the genital ambiguity. She was managed conservatively for chronic renal failure with end stage renal disease and hypertensive encephalopathy using antihypertensive. She was unable to commence dialysis and the cause of genital ambiguity could not be confirmed due to financial constraints before her demise. Conclusion: End stage renal disease is a rare preventable complication of AEG. The late presentation, ignorance and poverty were major contributing factors to poor outcome.

INTRODUCTION

Ambiguous external genitalia (AEG) are manifestations of Disorder of Sex Development (DSD). It is a term used to describe individuals whose external genitalia are deviant from the normal (intersex) with failure to categorize the sex of the child from the appearance of the external genitalia.[1]

AEG is classified into gonadal dysgenesis, male or female pseudohermaphroditism or true hermaphroditism[1] The latter is rare, seen in about 10% of cases of ambiguous genitalia.[2] Male and female pseudohermaphroditism are referred to as 46XX and 46XY DSD respectively and true hermaphroditism as ovotestisticular DSD. AEG may be due to masculinization of a female (XX) infant or under-masculinization of a male (XY) infant.[3] It is usually caused by genetic, enzymatic or chromosomal defects. [4, 5]

The prevalence and incidence of ambiguous external genitalia amongst newborns have not been well documented in developing countries, however in studies done in developed countries, a prevalence of 1-1.7% have been reported amongst newborns.[6, 7] In Enugu state, Nigeria, a high prevalence rate of 6.8% of congenital aberrations of external genitalia which was undiscovered by birth attendants or parents was noted among secondary school students.[8]

In developed countries, inutero diagnosis and availability of diagnostic facilities have aided early detection and proper management of AEG without complications.[9,10] Unfortunately, in resource poor countries, varying age at presentation and late diagnosis occur due to poor awareness of AEG by some clinicians and parents, coupled with limited diagnostic abilities and facilities [5,7] Most patients with AEG who are not discovered at birth rarely seek medical attention and may present later with various complications including precocious puberty, infertility and urinary outlet obstruction.[5]

We present a case of 16 year old patient with ambiguous external genitalia who was admitted with urine outlet obstruction and end stage renal disease. This case highlights the low awareness of this condition in our environment and the challenges encountered in the management with review of literatures.

CASE REPORT

A 16 year old patient admitted into the Children Emergency Ward with complaints of abnormal external genitalia and

difficulty in passing urine from birth, vomiting of one week and convulsion of day duration.

The external genitalia was noticed to be abnormal since birth but father had reared the patient as a female. She had difficulty in passing urine with straining on micturition and dribbling urine from birth. The difficulty in micturition worsened 3 days prior to presentation as she strained more than usual and cried out in pain while passing urine. She vomited 2-3 times daily, provoked by feeding, non projectile, non bilious and non-bloody.

The patient had one episode of generalized tonic clonic seizure a day prior to presentation. It was the first episode of convulsion in patient's life. The convulsion was sudden in onset, afebrile and associated with gnashing of the teeth and upward rolling of the eyes. It lasted about 15 minutes before it aborted spontaneously without loss of consciousness. Mechanical pressure was applied on the jaw during convulsion. There was no history of having sought medical attention for AEG until the present complaints of convulsion.

The antenatal history could not be obtained for any history of maternal illness in pregnancy or drugs ingested in first trimester. She was delivered by a traditional birth attendant and never received any immunizations. She was yet to attain menarche. Her motor and mental developments were normal, and she was in junior secondary school year 3.

She was the 6 th of 7 children of mother (6 alive) in a polygamous setting. Father had 19 children from 4 wives, (14 alive, 5 died immediately after birth). Her mother was the first wife and she was a 40year old farmer with no formal education. No family history of congenital abnormalities or ambiguous external genitalia in siblings. The review of systems revealed anorexia, urgency and hesitancy.

On examination at presentation, she was small for her age, had bilateral purulent eye discharge, moderate pallor, swollen lips and cheeks (due to pressure applied on the jaw during convulsion), and no signs of dehydration. Her height was 145 cm, weight 36kg, and BMI 17kg/m^2

She was conscious, restless and had normal tone in all limbs. Cardiovascular examination revealed tachycardia, with a pulse rate of 130 beats per minutes, blood pressure of 170/100mmHg and normal heart sounds. She had an ulcer measuring 2x2cm with a dirty base on the lower third of the left leg. Abdominal examination showed a scaphoid abdomen, bladder was not palpable and kidneys were not ballotable.

Genitalia revealed the fusion of the labia majora and minora, hypertrophy of the clitoris which had retractable skin (hood), with an opening at the tip of the clitoris which ended blindly (fig 1 &2). Attempts at catheterization of the opening failed. There were no palpable gonads in the inguinal area. Pubic and axillary hair development was at Tanner stage II and breast development at stage III.

A diagnosis of ambiguous external genitalia (AEG) with chronic renal failure and hypertensive encephalopathy was made. AEG was considered to be due to congenital adrenal hyperplasia (CAH).

Urgent PCV was 17%, bedside urinalysis showed blood 3+, massive proteinuria 500mg/dl, specific gravity 1.005 and pH 6.5. Serum electrolytes showed sodium of 143mmol/l, potassium 5.2mmol/l, and bicarbonate 11mmol/l. Serum urea was 46.7mmol/l, and creatinine 1,485mmol/l (16.9mg).

The Glomerular filtration rate (GFR) was 4.72ml/min/1.73m^2 using Schwartz formula.[11]

Chest x-ray showed osteosclerosis of the ribs, unfolding of the aorta and cardiomegaly of left ventricular preponderance suggestive of Hypertensive heart disease and renal osteodystrophy. Abdominal scan showed that both kidneys were echogenic with poor corticomedullary differentiation. There were obstructive changes with marked calyceal dilation worse on the right. The spleen, liver, gallbladder and pancreas were normal. Uterus, ovaries and bladder were not visualized due to inadequate bladder fluid and excess bowel gas.

Retroviral screen, HbsAg and Hepatitis C Virus were all negative.

Other investigations requested were buccal smear for barr bodies as Karyotype could not be done in our hospital, hormonal assay (pregnenolone, 17-OH-progesterone) to confirm CAH but they could not done due to financial constraints.

She was given a stat dose of Intravenous(IV) hydrallazine 10mg slowly over 15minutes, and maintained on oral hydrallazine at 10mg twice daily, tablet captopril 25mg twice daily, IV Zinacef 500mg 8hrly, tablet folic acid and fersolate. The blood pressure was monitored every 15minutes. Subcutaneous erythropoietin 1000units twice weekly was prescribed. The urologists were invited to assess

and repair the genitalia when patient was stabilized.

The patient was to commence haemodialysis at least 3times a week and be included in the dialysis/renal transplant programme for ESRD. However, due to financial reasons she was never dialysed and her condition continued to deteriorate. The medications were irregular with poor blood pressure control. On the third day she developed spasms, became unconscious with a Glasgow coma scale of 6 and she subsequently died on the 6 th day of admission.

Figure 1

Fig 1: Showing labial fusion absent urethral opening

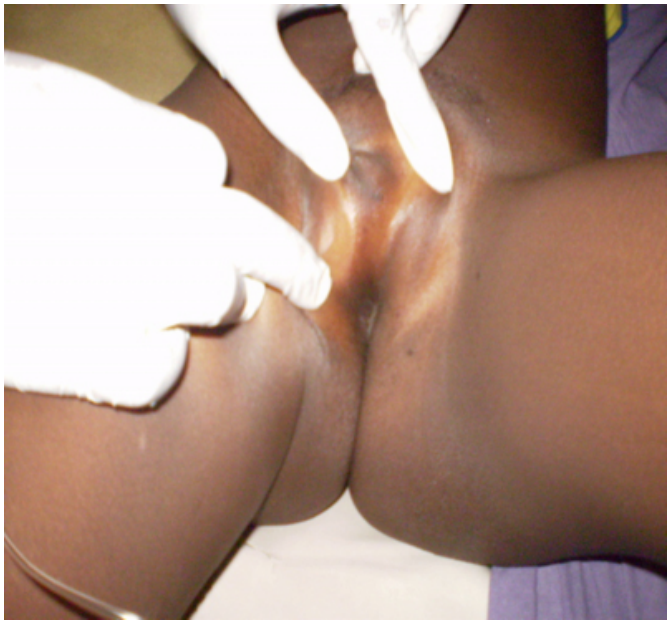
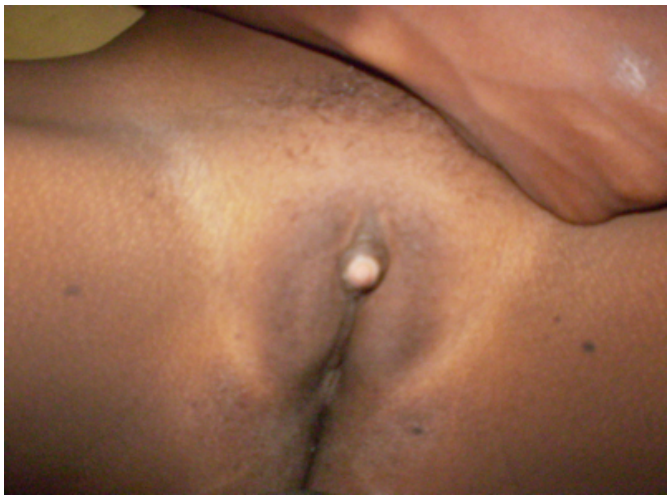


Figure 2

Fig 2: View of the external genitalia showing clitoral hypertrophy.



DISCUSSION

Ambiguous external genitalia are congenital birth defects that require a thorough and urgent evaluation. [5]The degree of ambiguity varies and manifests as a combination of hypertrophy of the clitoris, excessive fusion of the genital folds which obscures the vagina and urethra forming an artificial urogenital sinus which may become the urethra. Thickening and rugosity of the labia may bear some resemblance to the scrotum. The diagnostic criterion for the description of ambiguous external genitalia as proposed by Danish in 1982 is one of the most often cited in literature and is easily applicable in medical practice. [12]

There are different causes of ambiguous external genitalia; these include in female pseudohermaphroditism due to excessive virilization of female external genitalia, true hermaphroditism due to disorders of gonadal differentiation and gonadal dysgenesis and in male pseudohermaphroditism due to under virilization of the male external genitalia.[5] Congenital Adrenal Hyperplasia is the commonest cause of genital ambiguity in 46XX DSD.[3,13] It accounts for more than 70% of cases of AEG in genetic females.[13] CAH is caused by deficiency of the enzymes involved in the synthesis of cortisol and aldosterone of which the commonest is 21 hydroxylase.[14] Most cases of ambiguous genitalia due to CAH are sporadic and inherited as autosomal recessive conditions with a global incidence of 1:5000-16000.[12] The frequency is however highest in neonates of European, Jewish, Hispanic, Slavic, or Italian descent.[15] We considered CAH as the cause AEG in our patient, however, the diagnosis could not be confirmed due to financial constraints.

Although rare, genetic female virilization may be due to maternal drug ingestion. Virilization of a female fetus may occur if progestational agents or androgens are used during the first trimester of pregnancy.[16] After the first trimester, these drugs may cause only phallic enlargement without labioscrotal fusion. The incriminated drugs were formerly administered to avoid spontaneous miscarriages in patients who had a history of habitual abortion. We could not ascertain history of drug use in pregnancy by our patient's mother, and there was no family history of AEG in siblings.

Endocrine abnormality in the mother as a source of virilizing hormones is even rarer because these abnormalities, if initially present, usually prevent development of a pregnancy.[15] However, various ovarian tumors eg, arrhenoblastomas, Krukenberg tumors, luteomas, lipoid

tumors of the ovary, stromal cell tumors reportedly have produced virilization of a female fetus.[17]

DSD typically are diagnosed at birth in infants with ambiguous genitalia. However, age at presentation varies in developing countries. In developed countries with high level of awareness, diagnosis in-utero or at birth is prevalent making early gender assignment and corrective surgery possible before the age of sex identity. [7, 18]In sub regions with poor level of awareness such as Nigeria, many children with even major aberrations of external genitalia are missed at birth with some affected children reared along wrong gender line. Our patient was reared as a female and she eventually developed secondary female sexual characteristics. In a study[19] in Benin City, Edo State, in Southern Nigeria none of the females who had ambiguous genitalia was diagnosed at birth, the median age at presentation was nine years. Most of these children were delivered by traditional birth attendants and resided in rural areas. Our patient's delivery was also taken by a traditional birth attendant and the she had also resided with parents in the rural area. In a study from Mumbia in India, most children with ambiguous genitalia presented before the age of one year.[3] In another study from the Northern part of India, 70% of children presented after the age of 5 years.[20] This finding reveals the poor awareness of this condition in low resource regions and the need for more enlightenment because the numbers undiagnosed at birth by orthodox trained personnel were equally alarming.

Most patients with ambiguous genitalia who are not diagnosed at birth do not seek medical attention until they develop complications and are diagnosed incidentally as seen in our patient. Children with aberration who do not develop complications or whose parents/ caregivers are poor rural dwellers often do not seek medical attention.[7] In the study in Benin City, Edo State, surgical consultations were sought following accidental discovery while examining for other lesions in eight children by health workers. [19]

The finding of associated obstructive uropathy with consequent chronic renal failure was an uncommon complication of AEG. Our patient was brought to hospital for the first time because of end stage renal disease with a GFR of 4.72ml/min/1.73m^2 and hypertensive encephalopathy despite having AEG for 16years.

The exact cause of this associated genitourinary malformations are unknown however one explanation is that this may result from abnormally high androgen levels in utero.[21] Supporting this hypothesis is the observation that implantation of testosterone propionate in female rabbit fetuses results in abnormalities of the mesonephros.[21] Genetic variations in androgen sensitivity and biosynthesis have also been proposed to influence expression of signs of androgen excess in girls with CAH [22] and therefore could explain why some patients with CAH develop genitourinary anomalies and others do not. An integral relationship between gonadal and renal development has also been suggested by the identification of gene defects that cause abnormalities in both organs.[23, 24]

The evaluation of children with ambiguous genitalia is an emergency and requires immediate specialized care.[25] A rapid and organized evaluation should be initiated to develop information about karyotype, gonadal function, androgen biosynthesis and internal anatomy. Our patient was not referred for specialized care being delivered by a traditional birth attendant. Her parents also were ignorant and did not seek any form of medical help despite that the baby had urinary symptoms. This finding highlights the poor health seeking behavior in our environment.

The eventual cause of death in our patient was End stage renal failure (ESRF). The renal damage resulting from primary malformation of the genitourinary system in AEG with labial fusion and back pressure changes due to urinary obstruction may have caused the ESRF in our patient [26, 27] Late presentation, ignorance and poverty contributed to development of ESRF in this case.

Most children with ambiguous genitalia are born to parents unaware of the risk and with no family history of AEG as in this case. In families where parents have the trait for CAH, each child will have a 25% chance of being born with the disease. There is usually no harm to male fetus from CAH however in female fetus with CAH the adrenal glands begin producing excess testosterone by the 9 th week leading to virilization (urogenital closure and phallic urethra) which occurs between 8 and 12 weeks. The delivery of adequate amount of glucocorticoid to the fetus can reduce the adrenal testosterone production. At present, there are no programmes to screen for the risk in families who have not yet had a child with CAH. For families desiring to avoid virilization of a second child, the strategy is to commence dexamethasone as soon as pregnancy is confirmed and continue until the sex of the baby can be determined to be a male. The determination of an affected female can be done at 9 to 11 week gestation by chorionic villus sampling or by amniocentesis at 15-18 weeks gestation.[28]

In conclusion, AEG with urological abnormality is a preventable cause of ESRD. Whilst children with ambiguous external genitalia in developed countries survive and live normal life due to early diagnosis and proper treatment, the situation is different in developing countries. This case highlights an uncommon complication of ESRD following untreated AEG in our environment. There is need for early evaluation and treatment of children with AEG to avoid such complications including death.

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