Original Article

Genital Abnormalities and Management Outcomes as Seen in the University of Port Harcourt Teaching Hospital, Nigeria

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Abstract

Background: Genital abnormalities are a source of concern and anxiety to parents and patients and in some cases, for the physicians who may have difficulty making the pathological and eventually genetic diagnosis. They range from simple small penis and labial adhesions to complex genital ambiguity and disorders of sex development (DSD). **Aim:** The aim is to determine the genital abnormalities presenting in the Paediatric endocrinology unit of the University of Port Harcourt Teaching Hospital. **, Materials and Methods:** A retrospective cohort review of children presenting to the Endocrinology unit of the Paediatrics Department with genital abnormalities was undertaken from January 1, 2013, to December 31, 2017. The evaluation of the children included detailed history, physical examination, age and sex of rearing at presentation, clinical presentation, investigations, management, and outcome of treatment. **Results:** There were 31 children presenting with genital abnormalities of various kinds. Sex assigned to these children was 8 females and 23 males irrespective of complete pathological diagnosis. The median age of presentation was 13 months with a range of 0.1–168 months. The most common diagnosis was micropenis (32.2%) with various forms of DSD being the second-most common (29%) and most females had labial fusion (16.1%). Females with labial fusion had complete resolution following estrogen cream application, and 4 of the 7 children with DSD died. **Conclusion:** Making diagnosis and managing complex genital abnormalities like DSD in UPTH remains challenging because of the lack of diagnostic equipment and drugs, but simpler conditions have better and long-term outcomes.

Keywords: Children, disorders of sex development, genital abnormalities, Nigeria

Introduction

Genital abnormalities are a source of concern and anxiety to parents and patients and in some cases, for the physicians who may have difficulty making the pathological and eventually genetic diagnosis.[1-7] The incidence of genital ambiguity is rarely known in many resource-constrained countries where out-of-pocket modes of payment are the norm, so patients rarely take the initiatives of hospital visits until there is a real medical emergency as in the cases of salt-losing congenital adrenal hyperplasia (CAH). However, Ameyaw *et al*. reported a 28/10,000 live birth incidence in Ghana.[8] Labial adhesion has a reported prevalence ranging from 1.8% to 38.9% depending on the cohort being studied showing its relatively high incidence.[9-11] Hypospadias is relatively common in the paediatric male population with incidence ranging from 0.1% to 0.8% depending on the age of presentation and geographical location.[12,13] Labial adhesion is usually spontaneous and found incidentally as it rarely presents with any symptoms except when an infection precedes its presentation. It is estimated to be seen in about 3% of girls in their 2nd year of life with poor hygiene, low estrogen, and trauma as risk factors.[14,15]

The development of any human toward a well-formed male or female depends on the presence or lack thereof of testosterone and its functional entity.[16,17] Any human with testosterone and receptors that have an affinity to this will eventually have male external genitalia while the absence of this hormone and its

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functional unit will cause the genital tubercle to develop into a female. The male abnormalities can be simple hypospadias, undescended testes, micropenis, or a male with under virilized organ, while in the females, it could be a labial adhesion, clitoromegaly, or a combination of these latter features, in which case, a 46 XX disorders of sex development (DSD) is diagnosed.[6,16] DSDs are common in endocrine clinics and CAH is the most common cause of DSD with a prevalence of 1 in 1000–4500 live births.

In this particular research, we highlight the characteristics of patients presenting with genital abnormalities including those with ambiguous genitalia and the management protocols and strategies we have used to mitigate the parental anxieties and patients' ailments.

Materials and Methods

Study design

A retrospective cohort observational review of all children presenting to the Endocrinology Unit of the Department of Paediatrics, University of Port Harcourt Teaching Hospital was undertaken from January 1, 2013, to December 31, 2017. The hospital is a teaching and research center in the southern part of Nigeria. It serves as a primary and referral center to other hospitals in Rivers State and neighboring states such as Abia, Imo, Bayelsa, and Akwa Ibom states. The evaluation of the children includes a detailed history, physical examination, place of birth, age and sex of rearing at presentation, clinical presentation, investigations, management, and outcome of treatment/follow-up.

Ethical considerations

As a teaching and research institution, all patients are notified of the need to obtain consent for photography for medical illustration and all patients gave informed consent to have their photos or those of their wards taken. As this was an observational study, ethical approval for waiver was obtained from the hospital ethics committee.

Examination of genitalia

All patients had their genitalia examined in the nude after informed verbal consent was obtained from them and their parents or caregivers. Stretched penile lengths were measured using a wooden spatula placed at the dorsal base of the penis with the penis fully stretched minding the comfort of the patient. An assistant made a mark on the spatula at the tip of the penis and the distance between base and tip was measured using a nonstretchable tape rule. The urethral orifices were inspected and babies were made to urinate to observe the flow and orifice from which the urine flowed.

For clitoral length, all females were placed in frog-like position to expose the genitalia, and an assistant parted the labia majora to expose the clitoris. The main examiner then measured the clitoral length from base to tip using a nonstretchable tape measure that is graduated in millimeters.

Ultrasound scan tests

Ultrasound scan tests were done for all children by the institution radiologists to verify the presence or absence of gonads, uterus, abnormalities in the gonads, cryptorchidism, and the location of the gonads. Children who needed further radiologic evaluations were counseled.

Blood samples and hormone assays

Three-to-five milliliters of blood was collected from patients for measurements of hormone levels depending on the clinical and anticipated pathological diagnoses. Stimulation tests were done using standard protocols when needed and all patients gave informed consent for investigations. For patients in need of genetic testing, samples were sent to peripheral specialized laboratories for karyotype, and where possible, chromosomal analyses.

Results

In the five years under review, there were 31 children who presented with genital abnormalities of various kinds. Sex assigned to these children was 8 females and 23 males. The median age of presentation was 13 months with a range of 0.1–168 months.

Specific characteristics of genital abnormalities

For those patients with clinical and pathologic diagnosis as at the time of the research, the prevalence of each condition is shown in the bar chart in Figure 1.

Micropenis

There were 11 males presenting with micropenis with ages between nine months and 168 months with a median age of 121 months [Figure 2]. Two were infants, while the rest were adolescents and had a stretched penile length of between 2.10 cm and 4.60 cm, which were all less than the 5th percentile for their ages. Luteinizing hormone and follicle-stimulating

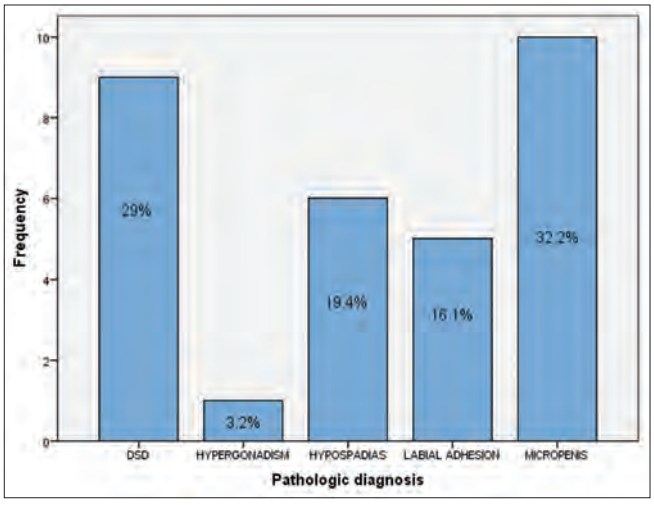

Figure 1: Pathologic diagnosis of clinical cases. The commonest diagnosis was micropenis (32.2%) with various forms of DSD being the second commonest (29%). Most of the females in this series had labial fusion (16.1%). DSD: Disorders of sex development

hormone (FSH) levels were normal in all of them, but testosterone was low in 7. Human chorionic gonadotropin stimulation tests done for these 7 showed an increase in testosterone levels for 5 but 2 failed to show increases and were suspected to have Klinefelter's syndrome. There was corresponding increase in penile lengths in 4 of them and two had constitutional delays in growth and they were reassured during counseling sessions. Following human chorionic gonadotropin stimulation, there was inferior descent of the testes into the scrotal sac. One of the boys, however, had retraction of the left testis and had an orchidopexy done by the paediatric surgeons.

Labial adhesion

There were five females presenting with labial adhesions with ages between 10 and 48 months. There was complete closure of the vaginal introitus and their clitoral lengths were between 0.2 and 0.4 cm. Two parents reported possible assault, but there was no evidence of trauma to the vulva. All of these had normal luteinizing hormone (LH), FSH, and estradiol, and with the application of estrogen cream, there was complete resolution of the adhesions and reopening of the introitus. Three months follow-up visits revealed no recurrence of the abnormality.

Hypospadias

Five children presented with hypospadias during the period under evaluation and their ages ranged from 0.01 month to 60 months and the median age of presentation was 13 months. The newborn had multiple congenital abnormalities and died from cardiac pathology, whereas the rest were referred to the paediatric surgeons for surgical management. The urethral opening of 2 of the patients was proximal and the remaining three were distal. Of the two with proximal meatus, one had cryptorchidism with the testes in the inguinal region. There was no other abnormality in the other body systems following careful examination. One child had urinary tract infection complicating his condition, for which he was treated with antibiotics.

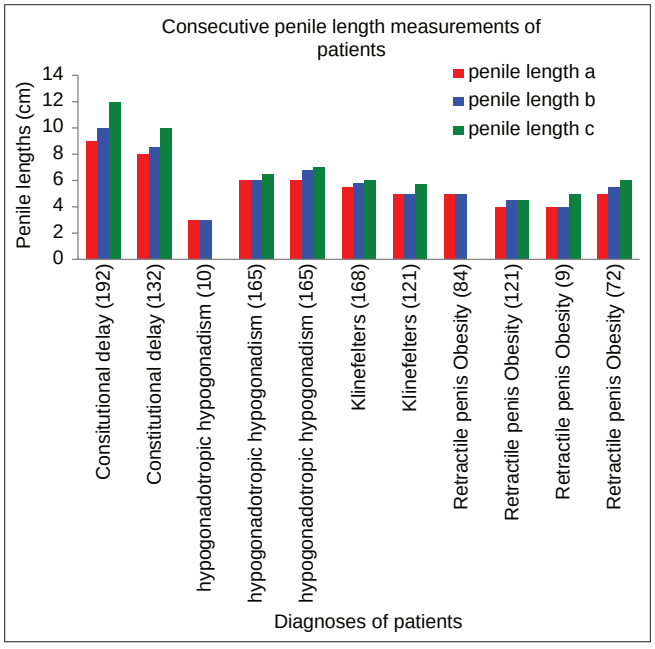

Figure 2: Bar charts showing diagnosis of children with micropenis and the progression in stretched penile length following interventions. Penile lengths "a," first visit, "b" first follow up, and "c" second follow up. The figures in bracket are ages of the patients in months

Disorders of sex development

Seven children had various forms of DSD including ambiguous genitalia, but one had normal genitalia with confirmed salt-losing CAH. Clinical diagnosis was possible for all children, but pathologic and aetiologic diagnosis could not be done for many. One neonate who had other multiple anomalies was suspected to have Smith-Lemli-Opitz syndrome and died soon after delivery [Figure 3]. One child had karyotype done, which revealed the absence of "Y" chromosome or SRY gene, 46 XX DSD, and has been on prednisolone due to scarcity of hydrocortisone. Three children who did not attend scheduled visits were later found to be dead following telephone contacts with their caregivers. The male with normal genitalia but salt-losing 21-hydroxylase deficiency was diagnosed following delivery and repeated shock in the neonatal period but also, a history of immediate older sibling death from 21-hydroxylase deficiency CAH.

Discussion

Micropenis or perceived micropenis is a source of concern for parents as there is the belief that reproductive function may be hampered by this "abnormality." Many children with micropenis do not present until their teenage years when there is social awareness among peers or following parental concerns.[1,18] Of the 11 males presenting with micropenis, only four were below the age 10 years, and these were reassured and followed up when it was noted they only had retractile penis with obesity. Retractile penis is common in obese boys as the penis gets buried in fat pads in the pubic region.[19] With

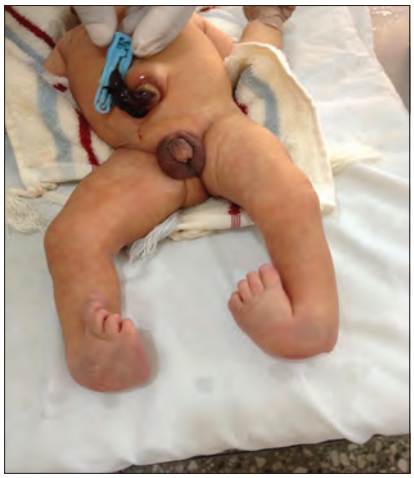

Figure 3: Atypical genitalia, bifid labioscrotal folds, enlarged genital tubercle, clubbed feet, and mottled skin

retractile penis, though the condition may seem benign, it can be complicated with psychological distress and infection if not properly taken care of. Patients are usually advised to lose weight and rarely will they need plastic surgery to remove the excess fat.[19,20]

One child had to be evaluated along the pituitary-gonadal axis because there were signs of Prader-Willi syndrome including voracious appetite and delayed motor milestones. He had hypogonadotropic hypogonadism following stimulation test and though samples were sent to Italy Mauro Baschirotto Institute for Rare Diseases foundation laboratory, they came back negative.[20] Micropenis is usually caused by decreased testosterone/dihydrotestosterone levels in utero and by a deficiency in gonadotropin and growth hormone levels.[21,22] Due to financial constraints, only seven children could have a stimulation test done to make the diagnosis of gonadotropin stimulation of the testes and response to this. For the teenagers who has micropenis due to pubertal delay, rise in testosterone and LH levels following the stimulation test indicates an intact pituitary–gonadal axis with the possibility of increasing penile length with age. However, our patients despite reassurance and increasing penile length were still not comfortable with the sizes of their penis as at the last measurements. They reported peer sneering and teasing and stigmatization and despite counseling about reproduction, erection, and virility, one questioned his options for surgical enlargement and reconstruction surgery.[1,23] This is not uncommon in this age group and has generated the debate of future sexual and reproductive capabilities.

Hypospadias was the third-most common genital anomaly presenting in our unit during this period and this is not unusual as it is the most common in many other units and surgical clinics in Nigeria. Many children with this condition usually present to the surgical unit of the hospital unless they are referred to the endocrinologists on suspicion of other endocrine abnormalities, which may be the reason the numbers are smaller than the general population. Like many other studies, distal urethral opening was present in our patients.[24] Distal hypospadias is less severe than proximal and for some, surgical repairs may not be necessary, especially when there is no skin deficiency ventrally or chordee, which was the case for our patients with distal hypospadias.[25,26] For mild forms of hypospadias, there are rarely genetic defects but for the severe forms, genome-wide expressions have revealed defects in some genes, especially the *HOXA4, IRX5, IRX6, EYA1*, and *DGKK*.[12,27] There are no laboratories in Nigeria to do genetic testing, but many environmental factors may have predisposed these children including but not limited to pesticides, paints, industrial solvents, and detergents. This risk must be explored when evaluating a child with hypospadias.[25]

Labial adhesion is a relatively common genital abnormality in the world with a worldwide prevalence of 2%, which is lower than a hospital prevalence of 6.6% in Jos Nigeria[11] and 16.1% in our study. However, the possibility of higher population prevalence should be stressed knowing that the condition is largely asymptomatic and not many parents look with scrutiny at the genitalia of their wards. In the past, female genital mutilation (circumcision) would have made this condition a lot more prevalent in the developing world, but with much public education, advocacy, and legislation to stop this tradition, the prevalence of labial adhesion from genital mutilation has dropped. Posttraumatic adhesion is high and rarely reported following sexual assault in this part of the world and though two parents reported this, there was no physical evidence of bleeding or fibrotic tissues in the vulva and vagina. Low estrogen levels have been reported to play a major causative role, but studies did not show a significant reduction in estrogen levels in children with labial adhesion as against their normal controls.[11,14] This is similar to this study where all patients had normal age-related sex steroid hormonal profiles. The clitoral lengths of these patients were within the normative levels in Ghana by Asafo-Agyei *et al*. and Nigerian children as reported by Jarrett *et al*.[28,29] In all patients, estrogen cream caused healing of the lesions with no recurrence and this is the mainstay of treatment as it softens the adhesion and eventually dissolves it.[8,14,30,31] Rarely is there need for surgical adhesiolysis, but this must be considered when there is infection of trapped debris, blood or urine or when the adhesion spans the full length of the vulva with the urethral opening trapped inside.

DSD is a relatively common paediatric endocrine in Nigeria and worldwide with a prevalence estimated at 1 in 20, 000, but those with 21-hydroxylase deficiency can be as high as 1 in 14,000–15,000.[6,8,16] The prevalence, however, varies from region and in Nigeria, no prevalence has been reported though several individual hospital estimates are known.[32] It was the second-most frequently occurring disorder in this report and most of these children presented in the early days of birth. Early presentation is common worldwide and in Nigeria, because of the anxiety associated with the inability to distinguish between male and female genitals.[20,32,33] There are already several reports on evaluation and management of DSD, and we followed the European Society for Paediatric Endocrinology protocol in many of our patients. However, many were unable to complete full medical workup and treatment because of financial constraints to pay for genetic, chromosomal, or some biochemical tests.[4] One child succeeded in traveling so many kilometers away from our facility to have a karyotype done which showed the absence of any Y chromosome or SRY gene. The high mortality rate in this report is mainly due to financial constraints to get the pathological diagnosis and treatment options with a lack of medications to keep the cortisol levels high enough for periods of illness or stress. A child with unexplained repeated shock in the neonatal and early infancy period should be investigated along the lines of CAH with urinary and serum sodium and 17-hydroxyprogesterone levels which are not usually cheap to assay, unlike other developed countries where they are done at birth as part of the screening process.[4,16]

Discussing cosmetic surgical repairs of the ambiguous genitalia must be with the full understanding that the sex of rearing is not an emotional decision, but a scientific one where the functionality of the genitalia and its psychological impact later in life can have a negative impact. The consensus among endocrinologists is to defer the repair until such a time when the child and parents can make joint informed decisions to avert gender dysphoria. However, in Nigeria where knowledge of this condition is only just coming to the fore, many parents are worried about stigmatization and social isolation and family separation as some believe since it does not run in their family, it must have been the spouse's family disease. The patient with 46 XX DSDS 21-hydroxylase deficiency has been counseled several times and the parents have accepted to delay the surgical repair until a later date not agreed upon yet. This is in keeping with several consensus statements concerning surgical interventions of children with DSD.[12,34-36]

Conclusion

In summary, managing children with genital abnormalities can be challenging worldwide and though some simple ones can be managed without many investigations, treatment or need for psychological therapy, others can cause great anxiety for the parents. Endocrinologists need to find all possible means to arrive at diagnosis and institute management protocols for the patients and the family. Advocacy groups should be inaugurated and patients referred to them so all of them can articulate their challenges and these can be worked on in group sessions or individually. Trained child psychologists should be incorporated into the team managing these children and unfortunately, these professionals are not many in Nigeria.

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Conflicts of interest

There are no conflicts of interest.

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