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Socio-medical burden of managing a Nigerian child with 46XY male disorder of sex differentiation: A Case Report

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Summary

Phenotypic expression of the male internal and external genitalia is due largely to the interplay between the proper differentiation of the bipotential gonad, the production of testosterone from the Leydig cells and the response of the undifferentiated external genitalia to Dihydrotestosterone. When any of the pathways involved in the mechanisms described above are distorted, it results in the 46 XY Disorder of Sex Differentiation (DSD). The incidence of 46 XY DSD ranges from 20 to 41% among the cases of Disorder of Sex Differentiation (DSD) in Nigeria, though there is a paucity of data on this condition. This report describes an under-virilized genetically male child who presented with ambiguous genitalia in the neonatal period and was subsequently diagnosed as SRY positive 46 XY DSD with reduced testosterone synthesis. This report is necessitated by the need to create awareness and highlight the relevant medico-social challenges in the management of DSD in a resource-poor setting.

Keywords: Chordee; Disorder of Sex Differentiation; Sex identity; SRY gene; Testosterone Synthesis.

Introduction

Disorders of Sex Differentiation or Differences in Sex Differentiation were formerly known as the Disorder of Sex Development, and it is defined as a condition in which the chromosomal sex is different from the phenotypic sex. This implies that the phenotypic sex cannot be classified as either male or female. [1] In Nigeria, where high premium socioeconomic value is placed on children (and in some culture, male children), the birth of a child brings relief of met expectations but when sex assignment becomes difficult or ambiguous, intense parental anxiety and problems of sex of rearing and in the future, problems of sex identity occur. This situation may set the template for intense social pressure, family strains and child abuse.

A case of 46 XY Disorder of Sex Differentiation refers to an individual with male genetic make-up with external genitalia that is not male or female. This condition is invariably diagnosed at birth and the clinical presentation varies depending on the degree of under-virilization. The literature on the prevalence of 46XY male DSD in Nigeria is scanty. Ekenze et al. [2] documented a
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prevalence rate of 41% for 46 XY types among children with DSD in Enugu Nasir et al. [5] reported a prevalence rate of 20%. In Ghana, [4] the incidence rate of DSD was 28 per 10 000 with only three of the infants diagnosed with 46 XY while a prevalence rate of 52.5% of 46 XY was reported among children with DSD in India. [5] In Denmark, an incidence rate of 6.4 per 100 000 live-born females with 46 XY disorder was reported. [6]

The phenotypic appearance of the genitals at birth is the outcome of the interactions between individual genetic constitutions, hormones and the gonads. The differentiation of the bipotential gonadal tissue into testes depends on the functional Sex Determining Region Y (SRY) gene encoded on the Y chromosome. The Müllerian Inhibiting Factor produced by the testes inhibits the development of the female internal reproductive structures from the Müllerian ducts. [7] At about the same time, testosterone produced from the Leydig cells of the foetal testes leads to the masculinization of the male internal reproductive structures. The undifferentiated foetal external genital develops into the male structures under the influence of Dihydrotestosterone (DHT); the latter is a product of the local conversion of testosterone-driven by the activity of the enzyme, 5α-reductase, and the high-affinity binding of DHT to the androgen receptors (ARs) located on the undifferentiated external genitalia tissues. [7]

Therefore, the 46 XY DSD results from: (1) the inability of the undifferentiated external genitalia to respond to Dihydrotestosterone (DHT) leading to Androgen Insensitivity Syndrome (AIS), (2) the deficiencies of enzyme required for the conversion of testosterone to Dihydrotestosterone i.e. 5α reductase deficiency, and (3) gonadal dysgenesis from inability of the bipotential gonads to completely or partially differentiate into testes: largely due to mutations of several sex-determining genes.

This report describes an under-virilized, genetically male child who presented to the hospital in the neonatal period and was diagnosed as SRY-positive, 46 XY DSD with abnormal (reduced) testosterone synthesis. The objective of this report is to create awareness among healthcare workers about a condition with huge medico-social implications in a resource-poor setting.

Case Description

The child, a presumably male, three-week-old infant was brought to the Paediatric Outpatient Department of Olabisi Onabanjo University Teaching Hospital, Sagamu, Nigeria, on account of indeterminate sex which was noted at birth. The child was registered at the clinic with a masculine name. There was no history of fever, vomiting, poor weight gain or refusal to suck at the breast. The pregnancy was achieved with the aid of a fertility drug (Clomid®). The mother, a 41-year old Para 0+2, registered the pregnancy for routine antenatal care in a private health facility at six weeks gestational age. The mother was admitted during the first and second trimesters on account of premature contractions and she subsequently received intramuscular Primolut-N® injections (containing norethisterone, a progestogen) due to history of two spontaneous abortions. The mother could not recall the number of doses received but the first dose was administered at 12 weeks estimated gestational age. The pregnancy was delivered at term via elective Caesarian section which was indicated by elderly primiparity with poor obstetric history. The baby cried immediately after birth and he was subsequently fed on breast milk substitute (NAN-1®) for the first three days of life due to poor lactation in the mother. Thereafter, the baby was successfully breastfed and also received BCG, OPV®, and HBV® vaccines.
The father was a 44-year old civil servant with an Ordinary National Diploma and a policeman while the mother was a secondary school teacher with B.Sc educational qualification. There was no history suggestive of consanguinity.

At presentation, the infant weighed 2.5kg (the birth weight was not known); further examination did not reveal any abnormality except a bifid scrotal sac with a palpable testicle in the left hemiscrotum (the right testicle became palpable at subsequent clinic visits), microphallus, chordee and penoscrotal hypospadias (Figure 1). The penile length could not be measured accurately because of the chordee.

The results of basal laboratory investigations were essentially within normal limits as follows:

Full Blood Count: White Blood Cells count – 9.37 × 10³/mm³; Neutrophils – 24.4 %; Lymphocytes – 55.3%; Eosinophils – 8.8%; Haematocrit – 33.3%; Platelets count – 420 x10³/mm³.

Serum Electrolytes, Urea and Creatinine: Potassium – 4.3 mmol/L; Sodium – 135 mmol/L; Chloride – 98.0mmol/L; Bicarbonate – 23; Total calcium – 10mg/dl; Urea – 11 mg/dl; Creatinine – 0.5 mg/dl.

Serum Testosterone – <0.03nmol/l (reference: 0.03-0.2nmol/l); Dihydrotestosterone – 248pg/ml (reference: 0-650pg/ml).

Sex Determining Region Y (SRY): The venous blood sample was reported positive for SRY genes. This indicated that Y - Chromosome material was found hence the child was reported as “most probably genetically male (i.e. XY)”. XO (Turners) and XXY (Klinefelters syndrome) were considered as possibilities. However, karyotyping showed that the chromosome pattern as 46 XY (Figure 2).

Abdominal ultrasonography showed indeterminate genitalia but both testes were visualized.

Further radiological evaluation of the child noted the absence of Müllerian structures with coexisting features of failure of phallus development and this informed the suspicion that the infant had reduced testosterone synthesis. The child was subsequently placed on monthly intramuscular injection of Testosterone at 25mg per dose from age of 10-12months for three months and an appreciable increase in penile length was observed (Figures 3a and 3b).

Thereafter, the child was referred to the Paediatric Surgical Team who made a diagnosis of Severe Hypospadias with marked chordee with a proximal penile meatal opening. He was planned for two-staged surgical repair; the first stage of the surgical repair had been carried out at the time of this report (Figure 4).
Disorder of Sex Differentiation is a very challenging condition to manage in our setting due to in part diagnostic handicaps, management skill and financial strain on the family. This case reflects the above and also the socioeconomic impact of this condition on family ties. The mother with monthly income of about seventy thousand naira was solely responsible for the cost of investigations and treatment (including non-medical cost of childhood upkeep) and has spent more than 60% of her annual income on the medical cum surgical management of her son with half of the amount spent on the first stage of surgery.
The 46 XY DSD results from complete or partial androgen insensitivity, enzymatic deficiency or gonadal dysgenesis as described by Swyer et al. in 1955. The demonstration of the SRY gene on the Y chromosome in the index child, palpable testes, low serum testosterone and normal DHT values with under-virilized external genitalia (with an increase in penile length following Testosterone administration) are very suggestive of reduced testosterone synthesis. It is plausible that the administration of norethisterone during pregnancy played a role in the phenotypic outcome of the external genitalia in the index case. Exposure of fetuses to female hormonal drugs in the intrauterine period has been documented to lead to urogenital tract malformations. In a retrospective cohort study carried out in Finland, the genital abnormalities encountered included hypospadias and hydrocele.

The socio-cultural value placed on childbearing as well as the socio-economic value placed on the male child in the Nigerian society would explain the parental choice of a masculine name for the child. At presentation, the suggestion of the need to adopt a gender-neutral name was rejected by the parents on account of religious conviction that the child was "male". The stance of the parents would have led to a crisis of sex of rearing and sex of identity in the future if the final sex of the child was not male. Therefore physician(s) or health workers present at birth or to who a child with indeterminate sex first presents must describe genitals with gender-neutral terms such as labioscrotal folds, urogenital sinus, and phallus or phallic structure. During the initial parental counseling, emphasis should also be on the adoption of gender-neutral names. This should be done as soon as possible to avoid unnecessary delays in the gender assignment decision-making process. The insistence of the parents of the index child on a gender-specific name, religious belief notwithstanding, may be related to the mother’s age and obstetric history including the parity, social pressures and the male sex preference in the society.

The father of the index child, who was a policeman, was absent in the management of the child, presumably due to the indeterminate sex of the child. This action placed a huge socioeconomic and emotional burden on the mother as demonstrated by several weeks of delay in getting funds for requested investigations. In particular, the karyotyping was done largely due to the serendipity of ongoing research in a sister institution, about six hours drive away. The choice of the distant sister institution was directly borne out of a search for reliable but cheap diagnostic facilities since the facilities were not available at our centre and the nearby commercial diagnostic services were too expensive for the family's socio-economic

Figure 4: The external genital at 19 months of age (two months after the first stage of Scrotoplasty)
capability. Also, it is worthy to mention that the mother's look-alike but older sister had to stand in for her in keeping clinic appointments because, out of the fear of stigmatization, could not disclose to her employer, the nature of her child's ailment warranting frequent hospital visits. Therefore, sociocultural factors can lead to delay in the presentation of children with DSD at specialist health facilities or cause non-compliance with hospital visits, requests for diagnostic investigations or surgical procedures, as earlier reported in a Nigerian child with Prune-Belly syndrome.\[13\]

Testosterone replacement therapy should be carried out if it is clinically or laboratory wise indicated. In this present case, testosterone replacement therapy achieved an appreciable increase in penile length, though actual measurement was not done because of the chordee. Also, surgical intervention for cosmetic and functional purposes was possible in the index child due to the availability of skilled paediatric surgeons and functional inter-departmental collaborations. This has proved to be essential in the management of the Disorder of Sex Differentiation.\[14\]

Conclusion

The management of Disorder of Sex Differentiation places a huge burden on both the parents and the healthcare providers. The availability of sound interdisciplinary collaborations, necessary diagnostic facilities and provision of psychosocial support to parents are essential.

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References


