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Sex Reassignment Dilemma in 4 Yemeni Siblings with Five Alpha-Reductase Type 2 Deficiency

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ABSTRACT

5α-Reductase two deficiency (5αR2D) is an autosomal recessive 46, XY disorder impacting the HeRD5A2 gene, causing ambiguous genitalia. Four Yemeni siblings with this condition sought guidance from the Sudanese Intersex Working Group (SIWG) in adulthood. A multidisciplinary evaluation was conducted, encompassing physical, mental, hormonal, and imaging examinations, although genetic mutation analysis of the srd5a2 gene was precluded due to limited facilities. Participants were initially assigned as females by an untrained birth attendant; the siblings later manifested virilisation before puberty, prompting a reassignment to the male sex. Despite presenting with 46 XY DSD due to 5αR2D, their sexual identity conflict led them to seek counsel from the SIWG. Comprehensive assessments confirmed the 5αR2D diagnosis. Extensive counselling with the family revealed their resolute decision to maintain the male sex despite concerns highlighted by the SIWG regarding future sexual function and fertility. This case underscores the significant challenges stemming from inadequate knowledge and interventions, emphasising the critical need for early diagnosis, proper genetic counselling, and expert management. Timely referrals to specialised facilities and consideration of options such as in vitro fertilisation (IVF) and preimplantation genetic diagnosis (PGD) for subsequent children are imperative. This report advocates for proactive measures in similar cases, emphasising the importance of tertiary care facilities for accurate diagnosis, informed decision-making, and optimal management of 5αR2D-related dilemmas.

INTRODUCTION

The disorder of sexual development (DSD) resulting from 5α-Reductase-2 Deficiency (5α-RD2) represents a rare autosomal recessive XY-DSD, leading to the inability to convert testosterone to dihydrotestosterone (DHT) (PA, 2006). While testosterone facilitates the normal development of the male testis and ejaculatory ducts, DHT guides the formation of the prostate and male external genitalia. The Deficiency of DHT manifests across a spectrum of phenotypes, ranging from under-virilised infants with conditions like hypospadias or micropenis to severe cases presenting with the appearance of normal external female genitalia (Witchel, 2018).

LITERATURE REVIEW

Determining the appropriate sex assignment at birth remains an intricate and contentious challenge for newborns with DSD, particularly those attributed to 5α-RD2 (García-Acero *et al.*, 2020). This complexity amplifies in developing countries, where labour attendants often misidentify the newborn's sex, frequently assigning them as female. Although initially labelled as female during childhood, these individuals experience virilisation during puberty, leading to gender misperception, dysphoria, and identity disorders in adolescence (David Sandberg, 2006). In underdeveloped nations where traditional untrained midwives predominantly oversee deliveries, severely under-virilised boys due to 5α-R2D are mistakenly assigned as female at birth and subsequently raised as such. However, upon puberty-induced virilisation, these patients and their families encounter diagnostic, treatment, and ethical dilemmas, considering the psychological implications, societal stigmatisation, and anticipation of local cultural and religious conflicts, the absence of medical expertise, comprehensive genetic analysis, and molecular diagnostic facilities exacerbates the plight of these patients residing in underdeveloped regions (Byers *et al.*, 2017).

The present report describes the experiences of four Yemeni siblings presenting severely under-virilised external genitalia due to 5α-R2D. All participants were assigned as female at birth by untrained birth attendants and consequently raised accordingly until the onset of virilisation during adolescence. The report describes the suffering journey of the patients and their families, the improper counselling of rural physicians, and the ethical dilemma on top of the social stigma.

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METHODOLOGY

The Yemeni parents sought assistance from the Sudanese Intersex Working Group (SIWG) for their four siblings, presenting a complex intersex condition and grappling with a disorder of sex identity. The siblings' ages ranged from 28 to 18 years old at their initial consultation. The SIWG adopted a comprehensive approach, delving into their medical history, conducting meticulous physical examinations, and evaluating their mental well-being. Various diagnostic modalities such as hormonal profiling, T/DHT ratio stimulation tests, ultrasound, MRI scans, and chromosomal analyses were employed. Despite the diverse phenotypes observed among the siblings, the diagnosis of 5αR2D was established based on these evaluations. Subsequently, following extensive counselling, the family opted for a male assignment and agreed to a treatment plan devised by the SIWG. This plan encompassed a series of reconstructive surgeries, hormone replacement therapy, and psychotherapy sessions.

In the first case, the eldest sibling, a 28-year-old male educated through secondary school and employed as a Décor labourer, presented with concerns regarding abnormal secondary sexual characteristics. As per the family's account, his birth was overseen by his grandmother at home, resulting in female-like external genitalia and an erroneous female assignment. His behaviour displayed boyish inclinations during childhood, with an increase in aggression towards girls. By the age of 4, testicles became noticeable in the inguinal regions alongside a small penis. At 12, medical consultations and investigations revealed the absence of a uterus, and bilateral undescended testicles were confirmed via ultrasound. Subsequent sex reassignment and bilateral orchidopexy were conducted without residual psychological issues, which both the family and the community positively accepted.

The psychological assessment revealed a self-confident male individual, albeit with moderate anxiety and concerns about his genital size and future marriage. He displayed clear attraction to the opposite sex since pre-puberty, engaging in non-coital sexual activities yet denying any masturbation while expressing heightened excitement for pornography.

RESULTS

Physical examination of this individual revealed a male phenotype with typical male body hair distribution. External genitalia exhibited bilateral palpable testicles, hypospadias, and cordee. Hormonal levels, including FSH, T3, Testosterone, and TSH, were within the average male range. A stimulation test (hCG stimulation test) indicated elevated testosterone levels, while DHT levels remained unchanged. Imaging studies (ultrasound and MRI) confirmed the presence of a small prostate, reduced seminal vesicles, and bilateral testes, while no uterus, ovaries, or vagina were visualised. Cytogenetic analysis affirmed a normal male karyotype of 46, XY, as shown in Figure 1.

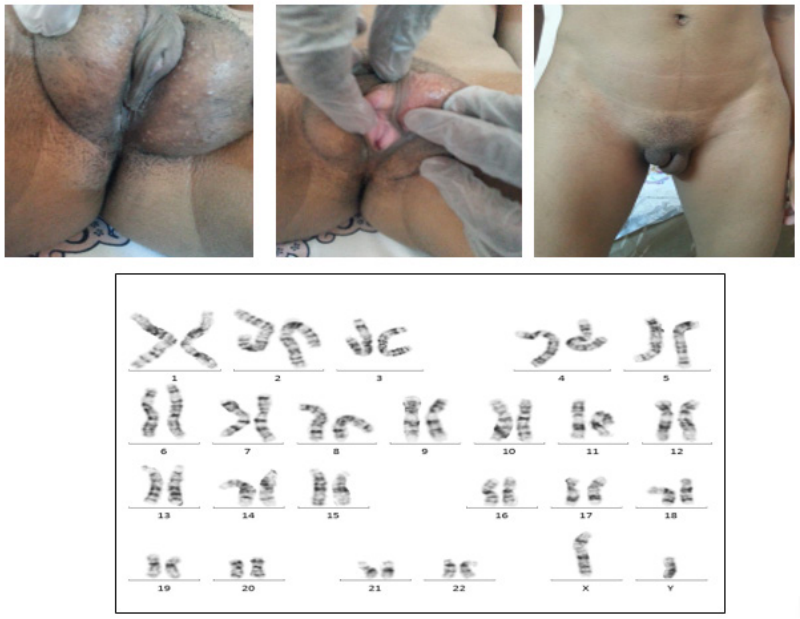

Figure 1: Depicts the external genitalia of case 1, illustrating a normal male karyotype (46, XY) with no detected cytogenetic aberrations.

The second sibling, a 22-year-old male, was delivered via normal vaginal birth at home, overseen by a traditional birth attendant (grandmother). The mother described the infant's genitalia as a small phallus embedded in a substantial clitoris-like prepuce, accompanied by hypospadias. Consequently, the child was assigned and raised as a female. By the age of 7, a Yemeni general practitioner reassigned the child as male due to bilaterally undescended testicles and advised consultation with a visiting medical team. Unfortunately, as per the history

given by the family, the visiting team performed a bilateral orchiectomy without seeking consent or providing counselling. Throughout childhood, the individual displayed boyish play preferences but denied experiencing erections, orgasms, or ejaculations.

The psychological assessment highlighted a coherent demeanour with pronounced irritability and preoccupation concerning sex assignment. No other abnormal behaviours, thoughts, or perceptual disorders were noted. The individual claimed attraction to females but admitted to having no sexual experiences or contact. Excitement upon exposure to limited pornography was expressed alongside claims of experiencing erections without ejaculation.

Physical examination revealed no facial hair, bilateral Tanner stage 2 breasts, absence of pubic hair, a faint surgical scar on the right labia-like structure and left inguinal region, absence of scrotal structures or testes, and a median clitoris-like structure concealing a small phallus under a prepuce, alongside a distal opening resembling a vagina. Hormonal evaluations displayed elevated FSH (46.6), LH (23.4), very low testosterone (1.2), and normal prolactin levels. Imaging studies (ultrasound and MRI) did not reveal the prostate, seminal vesicles, uterus, ovaries, vaginal ducts, or detectable testes within the inguinal region or intra-abdominally. Chromosomal analysis affirmed a male genotype, shown in Figure 2.

The third case involves a 20-year-old male, the third sibling, educated up to secondary school and employed as a pharmacy assistant. Born via normal vaginal delivery at home and initially assigned as female, signs of boyish play preferences and aggressive behaviour towards girls became apparent at the age of 4. Drawing from the experience with the elder siblings, the family noted the emergence of observable testicles, prompting consultation abroad, leading to reassignment to the male sex and subsequent corrective surgeries and orchiopexy.

The current examination unveiled a male phenotype with subtle facial hair development. External genitalia exhibited a well-developed scrotum, median raphe surgical scar, bilateral small testicles, a small penis with protruding glans, a well-developed prepuce, and hypospadias.

Hormonal analysis indicated normal male FSH levels (2.5mlu/ml), free T3 at 5.1pmol/l, normal TSH, and prolactin, with high testosterone levels (28.4nmol/L). Imaging studies revealed no uterus or ovaries, a 1.5 cm volume prostate on ultrasound, normal testes in scrotal cavities, and a micro penis on MRI. Cytogenetic analysis affirmed a normal male karyotype of 46, XY.

Mental status assessment depicted a mentally sound, well-adjusted, and self-confident young male without apparent psychiatric disorder. He acknowledged a positive attraction towards females, expressing excitement at seeing females in attractive attire or postures. During puberty, he experienced erections and ejaculation, denied homosexual tendencies, and reported no sexual experiences.Reconstructed male genital organs and observed musculature and pubic hair were noted,

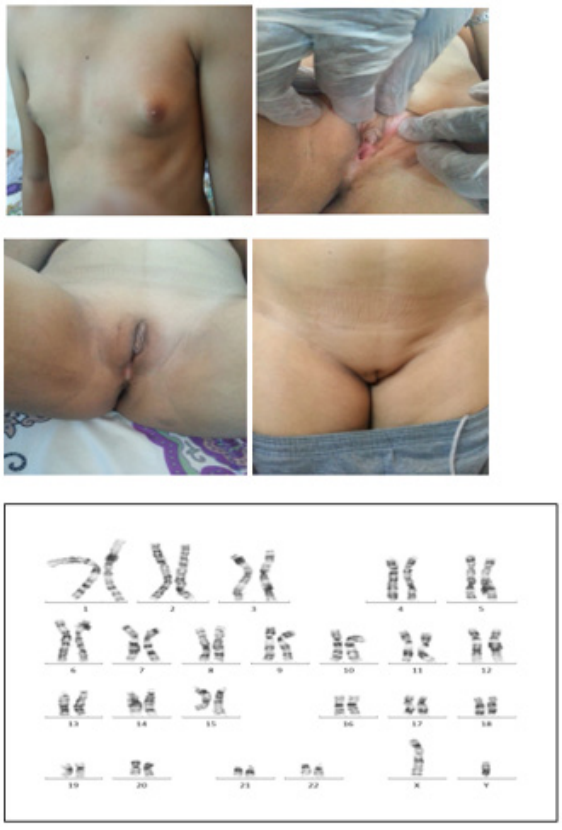

Figure 2: Illustrates the genitalia of case 2, displaying a Karyotype of 46, XY (with no cytogenetic aberrations detected).

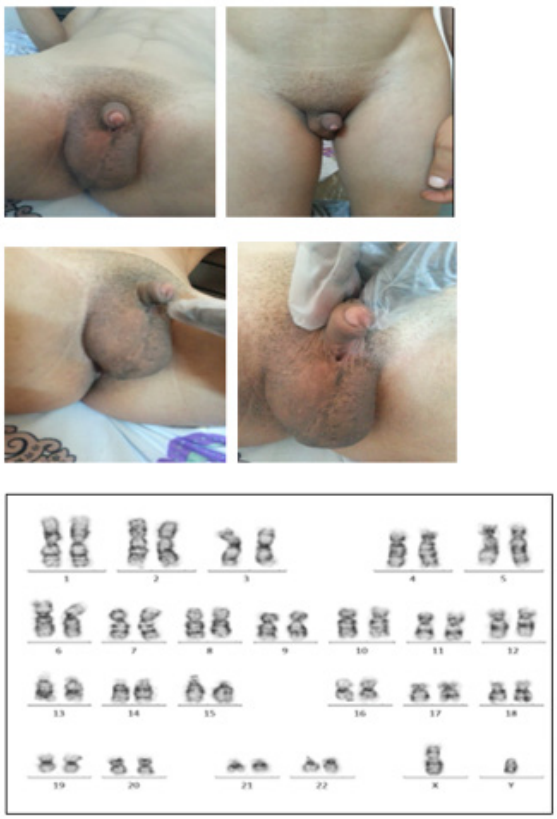

Figure 3: Depicts the genitalia of case 3 with a Karyotype showing 46, XY (no cytogenetic aberrations detected).

alongside the presence of hypospadias, as shown in Figure 3.

The fourth case involves an 18-year-old male, the fourth brother, who completed secondary school. Born via vaginal delivery at home attended by a traditional midwife, the patient displayed ambiguous normal genitalia and was initially assigned as female. During childhood, the mother observed the patient playing with both sexes, albeit with a preference towards boys. By the age of 3, observable testicles emerged, prompting the family to reassign him as male, with subsequent orchiopexy performed on the right testis.

Mental assessment depicted no observable mental disorder, with the patient displaying relative stability and self-confidence compared to his brothers. He exhibited a male sexual orientation, expressed a favourable attraction towards the opposite sex, and reported no sexual experiences.

Physical examination revealed a male phenotype with subtle facial hair and typical male pubic hair distribution. External genitalia exhibited a right inguinal scar, large labia-like scrotal structures housing palpable testicles, and an embedded median small penis with hypospadias and an obliterated vagina. Hormonal analysis indicated normal male values for FSH, Free T3, Prolactin, Testosterone, and TSH. Imaging studies revealed a 4 ml volume prostate on ultrasound, normal-sized bilateral testicles, and MRI confirmed these findings. Cytogenetic analysis affirmed male genotyping of 46, XY, as shown in Figure 4.

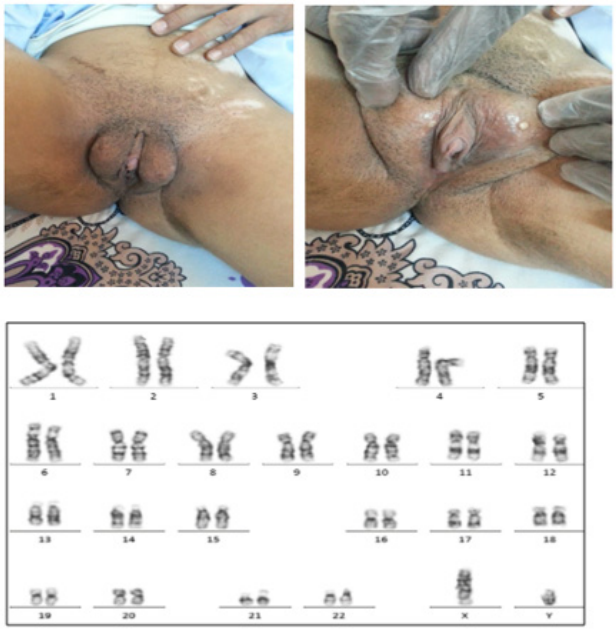

Figure 4: Illustrates the genitalia of case 4 with a Karyotype showing normal 46, XY (no cytogenetic aberrations detected).

DISCUSSION

The advancements in genetics, molecular biology, and imaging technologies have significantly revolutionised the understanding of Disorders of Sex Development (DSD). However, despite these breakthroughs, the complexities surrounding the diagnosis, sex assignment, and management of individuals with 5α-Reductase-2 Deficiency (5α-R2D) persist, particularly in regions with limited healthcare resources, such as Yemen. DSD, being multifactorial, presents challenges that extend beyond straightforward medical paradigms, encompassing intricate psychosocial and religious dimensions, thus aligning with the bio-psycho-social study model (Courtois *et al.*, 2009).

In a recent case study, all four siblings displayed ambiguous external genitalia at birth. Consequently, they were all designated as females, a decision made by a traditional birth attendant, who happened to be the siblings' grandmother. Her determination was based on her assessment of the relatively enlarged prepuce and the presence of a small phallus nestled within the inter-labia, which she considered to be the clitoris. Additionally, the identification of hypospadias was perceived as a vaginal opening. The presence of small scrotal sacs, in the absence of descended testicles, was interpreted as labia. Considering the birth attendant's lack of formal education, her sole experience gained through midwifery apprenticeship, and her limited exposure beyond her community, societal understanding excuses her decision regarding sex assignment. This circumstance is further reinforced by her esteemed sociocultural role as the matriarch of the family, entrusted with managing various aspects of women's affairs within the family structure, including arranged marriages, festivities, prenatal care, and childbirth. Consequently, societal norms prevent any challenge or intervention in her decision-making process from younger family members or men. The situation underscores the intricate interplay between traditional societal structures and medical understanding, emphasising the profound influence of cultural roles on decision-making within families, particularly in contexts where healthcare resources are scarce (Naezer *et al.*, 2021).

The patient history lacks documentation regarding the psychosocial elements, owing to the initial sex assignment and subsequent reassignment of the four siblings within a male-dominated rural community. The observable shift in behaviour, transitioning from perceived female to unmistakably male conduct, carries significant cultural implications in such communities. The compelling transformation in behaviour was a robust indication favouring the reassignment from female to male, albeit occurring belatedly, a change highly embraced within these communities. This transformation played a pivotal role in convincing the family to intensify their efforts in aiding their children, notably driven by the grandmother, who exerted considerable willpower to rectify the evident and recurrent misassignments. Consequently, despite the financial strain, the family was highly motivated and sensitised to seek both local and international medical advice. The latter venture was made possible through a restricted treatment grant. The family journeyed to Madinah, Saudi Arabia, where the initial author assessed the patients and linked them with the Sudanese Intersex Working Group. Subsequent medical evaluations, physical examinations, and investigations were conducted, inclusive of genetic counselling and appropriate management.

The eldest sibling underwent a series of medical consultations catalysed by the emergence of masculine behaviours. By the age of 12, the individual underwent orchiopexy, although further reconstructive surgery and suitable hormonal therapy are still required. No documented psychological disturbances were reported or perhaps concealed so as not to defame the grandmother.

The second sibling encountered a visiting medical team who inadvertently performed a bilateral orchiectomy, resulting in the absence of a testosterone source. This situation elucidates the minor development of female secondary sex characteristics, such as the absence of facial hair, second-stage Tanner breasts, a small phallus resembling a clitoris due to preputial resemblance, and the formation of a pseudovagina. Manifestations of sex identity disturbance were conspicuous during the mental state examination, revealing signs of irritability and excessive preoccupation with their assigned sex and future gender roles.

The psychosocial burden on the family reached its peak with the third sibling, compelling them to seek appropriate management abroad. Despite surgical reconstruction, inadequacies persist, particularly the need for hypospadias repair. This inadequate management emphasises the necessity for a multidisciplinary team to oversee the care of such patients.

The fourth sibling underwent reassignment at a younger age, experiencing a shorter period of genital ambiguity. By this time, the family seemed to have learned from previous experiences and observed the outcomes of early interventions. The youngest sibling underwent early orchidopexy, resolving the controversy surrounding their sex assignment. Notably, the age of reassignment to the male sex decreased successively from 12 to 3 years, indicating the family's evolving understanding and adaptation based on previous encounters.

The resulting responses were intricately linked to the cultural and psychosocial context of the community. The grandmother, a pivotal figure empowered to assign sex in the community as a birth attendant, held an unassailable position in her decision-making. The accumulated repeated process prevented overt psycho-social reactions in an attempt not to accuse the grandmother, which later depleted the economic resources of the extended family (1). This immense pressure compelled the family to seek additional nurturing solutions. The affected siblings endured the disorder's psychological strain for varying durations, with heightened stress both pre- and post-puberty. However, the resilient bond within the family provided a robust support system, absorbing much of the psychological impact and suppressing any negative reactions. Concern for the affected individuals was evident among extended family members, demonstrated through their generous contributions towards consultations and management, both locally and abroad.

The evident absence of a timely and accurate diagnosis, appropriate management, and inadequate counselling resulted in profound psychosocial trauma and dilemmas for the entire family. The Deficiency in foundational knowledge, genetic counselling, and ill-informed interventions may potentially lead to irreparable medicopsychosocial issues (Chatterjee, 2019). The possibility of In Vitro Fertilization (IVF) and Preimplantation Genetic Diagnosis (PGD) would have been a viable option for ensuring a healthy child, particularly starting from the second child, if the condition had been identified at the birth of the first child or even after corrective procedures (Ly *et al.*, 2011). In similar scenarios, healthcare professionals should prioritise referring families to centres providing genetic counselling, accurate diagnosis, and expert management to mitigate the risks of more affected babies and the complexities arising from incorrect sex assignment decisions (Suorsa-Johnson *et al.*, 2022).

As per previous studies, biochemical and imaging findings, performing mutational analysis of the SRD5A2 gene stands as the primary approach to confirm a diagnosis of 5α - Reductase–2 Deficiency definitively (Hamada *et al.*, 2012). Nonetheless, this diagnostic test is costly and often unavailable in many developing nations. Furthermore, the wide spectrum of phenotypes observed, even among siblings, complicates early and definitive diagnosis. The complexity of such disorders necessitates a multidisciplinary team approach. A successful model exists in Sudan, where the Sudanese Intersex Working Group (SIWG) undertakes the responsibility of assisting patients and their families.

In socio-religious contexts prevalent in underdeveloped nations, there is a prevalent inclination toward female-to-male reassignment. Unfortunately, suppose patients are not correctly diagnosed early. In that case, there is a risk of them falling victim to female genital mutilation (FGM),

which is still practised in some regions as a religious ritual performed on infant girls. Regrettably, suppose a baby boy with 5α-R2D is mistaken for the female sex, similar to many cases of FGM conducted by non-medical practitioners. In that case, the consequence is a complete distortion of the external male genitalia through the mistaken amputation of the penis, presumed to be the clitoris and labia minora. Fortunately, despite enduring significant hardship, our patient avoided the lifelong consequences of FGM. The predicament for these patients and their families typically arises in adulthood when the patient fails to menstruate or develop typical female secondary sexual characteristics.

CONCLUSION

In conclusion, the case of these four Yemeni siblings with 5α-Reductase-2 Deficiency (5α-R2D) illuminates the intricate challenges surrounding Disorders of Sex Development (DSD). The complexities in diagnosis, sex assignment, and management in resource-limited settings underscore the vital need for early, accurate diagnosis, genetic analysis, and multidisciplinary care teams. Improved access to genetic testing, counselling, and expert care is crucial to prevent misdiagnosis and mitigate the profound psychosocial and medical consequences. Additionally, the case emphasises the urgency of raising awareness, enhancing medical education, and implementing culturally sensitive interventions to address the complexities faced by individuals and families affected by 5α-R2D.

Strengths and Limitations

The strength of this case report is that it is a comprehensive portrayal of cultural, medical, and psychosocial complexities in managing 5α-Reductase-2 Deficiency. The limitation is its restricted generalizability and lack of long-term follow-up data post-treatment for comprehensive assessment.

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