46XY Disorder of Sexual Differentiation in Five Generations: A Preliminary Report


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Abstract. This is a preliminary report of 21 members of an extended family having 46XY DSD in 5 generations. The salient features of the affected members and the mode of transmission is highlighted. It is observed that the disorder is transmitted by only male members of the family, all normal females through five generations have always given birth to normal offsprings, who in turn have produced normal children. All affected members have karyotype of 46XY. There is a wide variation in the phenotype of the affected individuals, ranging from a normal female to an ambiguous male. All the individuals reared as males and whom the author examined had unilateral or bilateral undescended testes, perineal hypospadias and a vagina. All had varying extent of Mullerian elements in their pelvis. Two of the individuals reared as females also had menstrual periods and were married, but had to undergo gonadectomy due to malignancy of the gonads. The incidence of gonadal malignancy was found to be 30% in one cohort. This is the first time that such a large number of 46XY DSD in a single family is being reported. Genetic studies of the normal and affected members of the family are not yet done, but will be undertaken in order to determine the nature of the underlying gene and its location.

Keywords: 46 XY DSD, Familial DSD, Gonadoblastoma, Mixed Gonadal Dysgenesis

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Introduction

A family having several members affected by 46XY Disorder of sexual differentiation (DSD) is described. The index case (Family A) presented with malignancy of abdominal gonad and was found to have ambiguous genitalia with perineal hypospadias and vagina. He underwent laparotomy with excision of both his gonads and a rudimentary uterus with adnexa. His left gonad was found to be replaced by seminoma/dysgerminoma and his right gonad had ovarian stroma. Subsequently his elder brother presented with gonadoblastoma of his scrotal gonad. Two children from the family, also 46XY DSD, reared as males, were brought to the author and underwent masculinizing genitoplasty and excision of abdominal gonads along with Mullerian tissue. Gonadal histology showed testicular tissue in one gonad but ovarian tissue could not be documented. Details of family history revealed that there were several members in the family affected by DSD. A visit to the small village from where the family hailed revealed several members who were seemingly DSD candidates. All these members were residing under one roof. A detailed history was taken and family tree drawn up, which revealed that the disorder was seen in several members spanning 5 generations. This paper describes the clinical, radiological and operative details of those affected members who were examined and treated and some who allowed only examination. Some members of this family separated from the parent family 5 generations back and are living in another locality in the same village. A visit to the latter’s house showed that there were more affected members there as well. Blood samples of 10 of the affected members have consistently shown 46XY karyotype. Thirty three percent of the affected members of the family of index case have had gonadal malignancy.
Materials and Methods

Case 1: The index case was 17 year old reared as a male and presented with a lump in abdomen and loss of weight. His examination revealed male habitus, no facial hair, scant axillary hair and ambiguous genitalia. His stretched phallic length was 4.5 cms; he had ventral chordee, and empty labioscrotal folds. Gonads were not palpable in the inguinal region, and he had a hard lump in the suprapubic region and another in the epigastric region. The urethral opening was in the perineum and he also had a vagina (Fig. 1). Investigations revealed the following: Karyotype was 46XY, genitogram showed a capacious vagina without a cervical impression. FNAC of the suprapubic lump was suggestive of seminoma. He received chemotherapy and was operated after 3 cycles. He was found to have a seminoma/ dysgerminoma of his left gonad. His small right gonad showed ovarian stroma but no Graafian follicles. He had a rudimentary uterus and two fallopian tubes.

Case 2: A year later, the elder brother of the index case presented with malignancy of his right scrotal gonad. He had a male phenotype and had good facial hair (Fig. 2a). His left gonad was not palpable. He had, like his brother, a perineal hypospadias and a vagina, which, on genitography showed a uterus and a fallopian tube (Fig. 2b & Fig. 2c). Operative findings showed a uterus, two fallopian tubes and a gonad. The abdominal gonad showed ovarian stroma and the scrotal tumour was reported as seminoma as some testicular tissue was also seen. The latter showed hyalinised tubules.

Case 3 & Case 4: A year later, two children from the family, both nephews of the index case were brought for surgical correction of their ambiguous genitalia. Both had been reared as boys. Case 3 had right descended gonad, the other being nonpalpable. He had a vagina and his urethra was opening in the perineum (Fig. 3a). Laparotomy showed absence of uterus, there was a tube on the left side with a gonad attached to it, which was reported as immature ovary. Biopsy from the scrotal gonad showed normal testicular tissue.

Case 4 had bilateral nonpalpable testes and a perineal hypospadias with a vagina. Laparotomy revealed absent uterus, there was a tube with gonads at either end; the right one appeared to be like testis while the other looked like a streak gonad (Fig. 3b). Testicular tubules were seen from the right gonadal biopsy while the left one showed ovarian stroma. Both the boys had their abdominal gonads and Mullerian elements excised. They both underwent masculinizing genitoplasty.

The author visited the small village from where the family hailed, in the interiors of Maharashtra and saw that the entire extended family comprising of several cousins and their families were all living under one roof. Details of affected members in the family and their place in the family tree were obtained from the senior members of the family. One affected
individual agreed to be examined (Case 5). She looked about 40 year old, had coarse facial features, good breast development and female genitalia (Fig. 3c & Fig. 3d). Gonads were not palpable. She had sparse pubic hair and had never menstruated. Her karyotype was also 46XY. There was another affected individual, belonging to the 4th generation, who was interrogated by the author but refused to be examined. Reared as a female, she was in her 20’s, looked like a female, was petite, had fairly good breast development, and female habitus. She had attained menarche, was married to her aunt’s son, and subsequently was operated for bilateral gonadal malignancy. She had undergone chemotherapy and was following up at a cancer hospital regularly. She apparently had two siblings with the disorder; both were reared up as females. The elder sibling, in her forties was not available to see or examine, and her younger sibling had died in her late teens of gonadal malignancy. The family tree was drawn based on information gleaned from the elders in the family. (Fig. 4) Observations

In the family of the index case, referred to as “family A,” the total number of affected members were 12, seven of whom were reared as females, while 5 were reared as males. There did not appear to be much ambiguity of the external genitals in those reared as females as seen from fig. 3, and from the fact that two of the affected individuals were married and having marital sex. On the other hand, all the members brought up as males had severe degree of hypospadias, presence of vagina, varying extent of Mullerian structures and unilateral or bilateral undescended gonad. Four 33% of the 12 affected members had malignancy of their gonads.

Case 7, was the “daughter” of case 6’s cousin brother. 22 yr. old, reared as a female, she had not menstruated till age of 18. She was given hormonal treatment for three months, after which she started menstruating regularly and also developed breasts. She got married at the age of 20 yr., and stopped menstruating after two years of marriage at which time her pregnancy test was negative. During course of investigation for her primary sterility, she was found to be 46XY. Laparoscopy showed what appeared like bilateral streak gonads which were excised. The histology report showed bilateral gonadoblastoma.

Second visit to this family revealed 4 more affected members. The first (Fig. 6a) was the paternal "aunt"of case 6. The other three were siblings related to the former, the exact relation could not be defined, however they all had the same family name. All four were reared up as females but were looking like DSD individuals (Fig. 6a, Fig. 6b, Fig. 6c and Fig. 6d). Three "ladies" were over 60 yr. of age and the author could not examine them, and the fourth "woman" in her thirty's refused to be examined. They were all unmarried, none of them had had menstruation, but they did have some breast development. They allowed their blood to be collected which confirmed 46XY as their karyotype.
Fig. 6.  **Fig. 6a. Clinical photograph of the unmarried aunt of case 6, who also had karyotype of 46XY; Fig. 6b, Fig. 6c, and Fig. 6d. Clinical photograph of three siblings, all 46XY, related to family B.**

Another interesting feature that was noticed was that the affected members seemed to be quite content and not disturbed about their physical state. The phenotypic females were going about their normal household chores like other normal females. The normal inhabitants in the family were also treating the affected ones as normal. None of the affected members had ever expressed a desire for a sex change.

In the second family (now referred to as family B), the cousins four or five generations back have separated from each other and are living in separate houses in the same village. However, the author visited only one house and is still in the process of getting more details of the affected individuals from the other houses. The data gathered so far shows that there are in all 9 affected individuals in family B, seven reared as females and two as male. Two 22% of these have had malignancy of their gonads.

The transmission of the disorder was seen to be only through male members. All normal females have always borne normal children. Third generation appears to have skipped the disorder in family A (Fig. 4). Secondary sexual characters were found to be variable in male phenotypes. Graafian follicles were not demonstrated in any of the gonads ruling out the diagnosis of ovo-testicular DSD.

The incidence of gonadal malignancy in the index case family was found to be high. There is no history of consanguineous marriage in the family except for affected individual no. 6 in the family tree chart (Fig. 4), from 4th generation who married her aunt’s son, but after marriage, had malignancy of her gonads and bore no children.

**Discussion**

The family described in this paper is unique for several reasons. Firstly, the sheer number of 46XY DSD seen in this particular village is very high. The author could get details of the family tree only from one large joint family of the index case referred to as Family A, and smaller families of case numbers six and seven referred to as Family B. The latter two cases belonged to the family that had branched off from the family A five or six generations back. There are several more families which are branches of family B, having members of their families affected with this disorder. Figures to link all these multiple families in one composite pedigree diagram is not possible at present, as details of all the family trees of the other families are not known so far. It should be stressed here that getting to interview and talk to the affected individuals has been a daunting task because not all affected members or their families are willing to be interviewed. However, it is clear from the members studied so far that the disorder is transmitted only by male members of the family, who appear to be normal individuals. All normal females in the family have always borne normal children and grandchildren. None of the normal females in all the five generations have given birth to a 46XY DSD. There is no history of consanguineous marriage in the families except for the one case mentioned earlier. The women who have married into this family are not from the same village. There is no obvious history of similar occurrence in the families of the women who have come into this family by marriage. Thus it would appear that the women in the family are not responsible for transmission of the disorder. The exact mode of transmission whether it is autosomal recessive or otherwise remains to be seen. The transmission is peculiar as a glance at the family tree shows that the third generation in family A, has completely escaped the disorder. Chromosomal analysis, DNA studies or gene defect has not been yet determined in this family. It has been well established that in individuals with 46XY DSD, where the gonads are dysgenetic, several different genetic mutations have been found.\(^{1,2}\) The possibility of a normal looking male being the carrier cannot be denied as the carrier may have mosaicism. The incidence of malignancy in the index patient’s family is 33%, that in the other two families is 22%. 

Familial 46XY DSD appears to be a rare phenomenon. A report cited in Endocrine abstracts from Argentina, reveals a cohort of 19 patients from five unrelated families having 46,XY DSD, where the authors have identified 6 heterozygous NR5A1 mutations and reported an autosomal dominant mode of transmission with variable penetrance.

Another publication, a research paper on 46XY female adolescents presenting with amenorrhea, describes 15 individuals having mainly female phenotype. Genetic studies in these revealed SF1 mutations of different varieties to be the commonest mutation in these individuals. It, however, remains to be seen how the disorder found in several members of a family through five generations and more has been transmitted. This will need extensive and in-depth genetic study. This is a preliminary report. A clearer picture will emerge after collecting more data from the village and subjecting their blood samples for detailed genetic mapping. This is not possible in India at present and will need collaboration from geneticists elsewhere to carry this very intriguing project to its completion.

Conclusions

46 XY DSD (mixed gonadal dysgenesis) in 21 individuals, all belonging to one extended family has been reported here. The affected members showed wide variation in their phenotype. The incidence of gonadal malignancy was 33% in family A and 22% in family B. The disorder appears to be transmitted only by male members of the family. All normal females in all the 5 generations have borne normal children and grandchildren.

References

