45 XO/46 XY Male with Deletion of Long Arm of Y chromosome: A Rare Cause for Ambiguous Gender

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Abstract
Disorders of sex development are among the most complex conditions for which many a time no definitive cause can be found. The birth of a child with ambiguous genitalia represents a big challenge and a multidisciplinary team is required for the diagnosis and management of these patients. We present a case of a 5 year old child whose external genitalia were not well formed and he presented with undescended testes. His ultrasound showed presence of both testes in deep inguinal ring and small left sided uterus. Developmentally and intellectually the child seemed fine for his age. He was initially brought up as a girl but was upset and felt himself misfit and when he was dressed and made to play with boys his personality changed altogether and he became a lively cheerful child. He was referred for cytogenetic studies and showed 45XO karyotype in 90% metaphases and 46, Xdel(Yq) in 10% metaphases with a small Y chromosome having a significantly deleted q arm.

Key words: Ambiguous Gender, Mosaicism, 45XO, Deletion, Gonadal Dysgenesis, Y Chromosome

Introduction
Disorders of sexual development are heterogeneous group of disorders of sex determination and differentiation. The term mixed gonadal dysgenesis is sometimes used for this group. ‘Gonadal dysgenesis’ means inadequate development of the gonads also known as Disorders of Sex Development. These are among the most complex conditions encountered by the clinician and in many patients no definitive cause for the disorder can be found. Therefore the birth of a child with ambiguous genitalia still represents vast challenge. Normal human beings has 46 chromosomes (in 23 pairs, 22 autosomes and 2 sex chromosomes). Females have two X chromosomes and males have an X and a Y chromosome in their cells to give them normal gender differentiation. This results in 46, XX karyotype in females and 46, XY karyotype in males. However people with 45, XO/46, XY mosaicism have two different types of cell. One type contains a single X chromosome. The other type contains an X and a Y chromosome. Some of the people with 45, X/46, XY karyotype have a variant form of Y chromosome with an unusual structure. The condition has different presentations. Some are female and have a form of Turner syndrome - that is, they are more like girls born with a 45, X genetic constitution. Some are apparently normal males and go unnoticed until puberty or later. Sometimes these individuals are born with ambiguous external genitalia that show incomplete development towards any side. Most children with 45,X/46,XY are apparently healthy, normal-appearing boys. Many of these boys commonly have no risks or problems from their genetic constitution. Of the normal appearing males, most will have two normally functioning testes. But one quarter to one third of them will not. One testis or both may be non-functioning, or one may contain mostly fibrous tissue with a small amount of testicular cells, or on one side there may be a non-functioning complete gonadal streak. In 45,X/46,XY the sexual differentiation into male is incomplete -mildly, moderately, or severely. Some people with a 45,X/46,XY karyotype have reduced fertility and some are infertile. No judgement can be made about fertility until well after puberty in the apparently normal males. Some of the male patients diagnosed initially as 45,X later have proved to have a structurally aberrant Y chromosome. Others have been found to be mosaic for a cell line bearing a normal or abnormal Y chromosome. About half of people with 45,X/46,XY have a structurally abnormal Y chromosome. In some of these cases, excess euchromatic material on an autosome has been found and interpreted as evidence of Y chromosome/autosome translocation. Part of the Y chromosome can be missing and there can be an extra copy of another part. Underlying the female: male difference is the presence or absence on the Y chromosome and more of the SRY gene. The SRY gene determines whether an individual baby will become male or female, with testes to develop in the first place, and they then produce the hormone testosterone. If too small a number of gonadal cells have the SRY gene, this results in the development of dysgenetic gonads. Overall, the effects are generally unpredictable, regardless of the form of the Y chromosome. The effects are believed to depend on multiple factors: the instability of the abnormal Y
chromosome, leading to a higher proportion of 45,X cells, the level of mosaicism in the gonads and other tissues, the 45,X cell line, the extent of the missing parts of the Y chromosome and to a lesser extent the extra parts. In particular, the presence or absence of the sex-determining SRY region is a key determinant. Not uncommonly there are more than two cell lines and this complicates the picture. Ambiguous genitalia are more common when the breakpoint is in the short arm. The ability to diagnose these conditions has advanced rapidly in recent years. A highly specialized team of physicians, surgeons and experts of psychosocial care is needed to counsel parents and patients accordingly. We present a case of a 5 year old child who was born with ambiguous genitalia and was referred to us for cytogenetic studies.

Case Report

In a far of village of Afghanistan a child was born to a couple about five years back. The child was the product of nonconsanguinous marriage, had four siblings and all were normal. There was difficulty in ascertaining the gender of the baby as external genitalia were not well formed. Since phallus was not properly recognizable and labio-scrotal appearance and urethral opening was such that the parents considered the baby as female and dressed her as such. As the baby grew she became withdrawn and would not talk much. The child obviously appeared misfit amongst the girls and would not participate in girlish games. The situation made her aloof and depressed. The parents noticed it and sought consultation of pediatrician who noticing the ambiguity in gender differentiation referred the patient to a Urologist in Islamabad. Considering it as a case of gender ambiguity with presentation of hypospadias, chromosomal analysis, hormonal profile and ultrasound abdomen and pelvis was advised. This was done to confirm the genetic makeup, hormonal status and internal genitalia of the child. Ultrasound findings suggested presence of small testicles under deep inguinal ring on each side. In addition, presence of a thin small uterus deviated towards the left side, suggested the possibility of unilateral uterine development (i.e. uterus unicorns unicollis). Chromosomal studies were performed on peripheral blood. Culture was established in PB Max medium and peripheral blood lymphocytes were stimulated with PHA (Phytohaemagglutinin) to undergo mitosis. Colcemid was used to arrest chromosomes in metaphase stage and then harvesting was done as per standard protocols. Twenty metaphases were analyzed after Gimsa- Trypsin banding. The results of chromosomal studies were very interesting as 90% of metaphases revealed 45 XO Karyotype with absence of Y chromosome. Only 10% metaphases revealed 46XY karyotype and that too with a significantly small Y chromosome (with a deleted “q” arm) as compared to a normal Y chromosome.

Discussion

Here we see that even if only 10% metaphases revealed a small deleted Y chromosome, while in 90% metaphases no Y chromosome was detected, it was still enough to cause formation of testes and male type differentiation. Initially the affected child was brought up as a girl but remained depressed and aloof amongst girls. Later when the child was dressed as males and made to play with boys, he became active and more playful and started participating enthusiastically in all such activities that boys older than him would do. His whole personality transformed and he became a happy child in place of that misfit, withdrawn and aloof kid. No doubt, “Birds of feather flock together”
Karyotype of the patient - 45,XO

As mentioned previously the clinical features of XO/XY “Mosaic intersex syndrome (MIS)” vary widely. Majority are females with some degree of masculinization depending upon the variable activity of the Y chromosome. Some cases of MIS are phenotypically male and show variable features. Some are true hermaphrodites with ovo-testis, some have gonadal dysgenesis (streak gonads), some are male pseudo-hermaphrodites with testicular tubular structures on both sides while some have only one gonad. Our case shows bilateral undescended testis (in deep inguinal ring) even though 90% metaphases showed 45,XO karyotype and only 10% of metaphases showed 46, X del(Yq) karyotype with a small Y chromosome having a truncated long (q) arm. It may be presumed that the testicular structures are determined by the presence of Y chromosome and the degree of intrauterine masculinization follows from degree of development of fetal testis. Later pubertal virilization depends upon the presence of adult type leydig cells. Deletion of long arm of Y chromosome may be associated with certain developmental problems e. g short stature. Some may also have ambiguous genitalia or undescended testis and some may be apparently normal and referred for infertility due to azoospermia. These features are however not simply correlated to the size of deletion. In our case external genitalia were not well formed and he had un-descended testes and thin small unicorunate uterus. He had Y chromosome in only 10% of cells and that too with deleted q arm. There have been case reports of males with 46 XX genotypes but male phenotype with 45 X0 and 46XY in only 10% of cells and that too with deleted Y arm have rarely been reported. In our country this underreporting is probably because of our cultural limitations and also because of paucity of facilities and high cost which is required for diagnosis of these disorders. In various case reports it has been proposed that part of the Y chromosome can be missing or there can be an extra copy of another part. Overall, the effects are generally unpredictable, regardless of the form of the Y chromosome. Some 45,X males originate from Y chromosome/autosome translocations following a break in the proximal long arm of the Y chromosome. In a male patient with a 45,X karyotype, the terminal part of the Y chromosome short arm may be translocated as a single block on to the X chromosome. This rearranged X chromosome, in every regard behaves the same as that present in XX males resulting from an abnormal X-Y interchange. There have also been case reports of nonmosaic 45,X male patients. Ambiguous genitalia are more common when the breakpoint is in the short arm of Y chromosome.

As with 45,X/46,XY, no judgement can be made until puberty about fertility in the apparently normal males. Various case reports with 46,XX males, 46,XX/46XY or even 49XXXXY males have been reported. This is because the testis-inducing SRY (Sex-determining Region Y) locus which is normally located on the short (p) arm of the Y chromosome, can sometimes get translocated to an X chromosome during meiotic division of a primary spermatocyte. After having determined hermaphroditism, assignment of an appropriate gender becomes urgent. Traditionally, a multidisciplinary team of healthcare professionals comprising of paediatrician, paediatric endocrinologist, paediatric surgeon and paediatric psychiatrist have meetings with parents and the gender of the affected individual is assigned based on genital, gonadal and genetic factors. The process by which gender is assigned to intersex case is based on the concept that children are gender neutral at birth and can be made to assume male or female characteristics through a combination of psychosocial counseling and appropriate hormonal and surgical treatment. In all such cases the baby will be thoroughly examined. Ultrasound abdomen and pelvis (and CT scan if required), hormonal profile and cytogenetic studies need to be performed. There may be a need to take a biopsy from the gonads. Combined information from all these sources helps to determine the child’s underlying gender. A decision then needs to be made whether to bring up the baby as a girl or a boy based on the discussions between doctors and parents. It is occasionally not entirely clear whether the baby, while growing up, will come to see itself as a girl or a boy. People who have been through the boy: Girl decisions suggest that any surgery is likely that some reconstructive surgery will be needed. There must be adequate functioning gonadal tissue present to sustain and develop sex characters, and gonads producing contradictory hormones should be excised. As malignant growth occurs in 1.91% of true hermaphrodites, most commonly arising in dysgenetic or undescended testes, the long-term follow-up and screening particularly for testicular neoplasms is suggested. As with 45,X/46,XY, no judgement can be made until puberty about fertility in the apparently normal males. In our case the child did not have well defined genitalia but he had both the testis and a small unicorunate uterus. He was subjected to hormonal and
chromosomal analysis and urogenital evaluation by a Urologist and a Paediatric Surgeon was done.
It is thus suggested that cases of ambiguous gender should be managed well in time to avoid psychological trauma both to the child and other family members and various educational programmes to understand the psychological and social implications of these cases of gender assignment should be conducted.

References