

# Ambiguous Genitalia: A Case Report

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**Abstract:** When the sex of the newborn child cannot be decided then it is called as ambiguous genitalia. This becomes very much stressful and serious condition for parents and doctors for which immediate and multidisciplinary approach is expected. Hormonal and genetic factors play crucial role in disorder of sex development. **Case:** We present a case of ambiguous genitalia with omphalocele. Blood sample of new born baby was sent to Cytogenetic laboratory for sex determination. Along with ambiguous genitalia, omphalocele, presence of uterus and testis on sonography, patent ductus arteriosus was present. Karyotyping was done which revealed 46, XY, add 5p (15.3). The hypothesis of relation between karyotyping report and clinical symptoms is presented in this case. **Conclusion:** Karyotyping is a gold standard method in case of ambiguous genitalia.

**Keywords:** ambiguous genitalia, omphalocele, sex determination, chromosomal aberration

## 1. Introduction

Ambiguous genitalia is defined as disorders of sex development, constitute a complex, major social and medical emergency<sup>1</sup>. In such condition, instead of guessing the sex of the new born baby, process of commencement of investigations should start as early as possible. Team of paediatrician, endocrinologist, psychiatrist, geneticist and surgeon should gear up to plan the whole treatment and management of the case and give assurance to the parents. It is imperative to determine the etiology as early as possible when ambiguity is noted<sup>2</sup>.

Sex determination is a complex process and is one of the results of fertilization. The formation of male or female external genitalia results from a number of events starting with sex determination and progressing through differentiation of internal and external reproductive structures after zygote is formed. While the inability to proceed through sex determination and differentiation in a usual manner is referred to as a disorder of sex determination<sup>2</sup>. Etiopathogenesis of ambiguous genitalia along with omphalocele is discussed in this case report.

### Case Report (photograph no. 1)

32 weeks preterm born via Caesarean section was admitted to neonatal intensive care unit for respiratory distress and protrusion of abdominal organs from umbilical cord. Weight-1.8 kg, height- 47 cms, Head circumference- 34 cms

## 2. On sonography- (photograph no. 2)

Prepubertal status of uterus was noted, 1.7 x 0.8 x 0.4 cm

Bilateral ovaries poorly delineated, two well defined echogenic structures were noted each in the bilateral inguinal areas at lower end with evidence of internal vascularity likely testis.

A 4-mm defect was noted in the umbilical region content being bowel. Rest of the structures are WNL.

## 3. On 2D – ECHO

2D Echo was done suggestive of acyanotic heart disease: small sized ostium secundum-atrial septal defect with patent ductus arteriosus (PDA).

## 4. Investigations

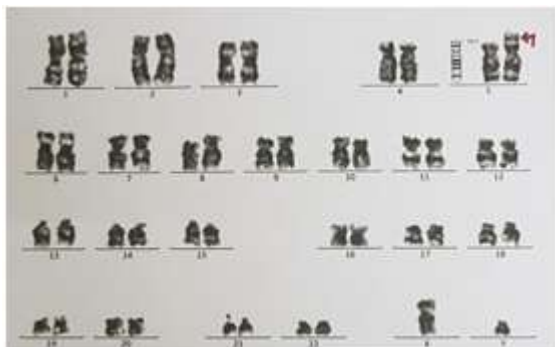
- 17-OH progesterone was mildly raised (3.7ng/ml).
- Karyotyping of the baby showed 46, XY with extra genetic material of unknown origin on p arm of chromosome number 5 (photograph no. 3).



Photograph no. 1 shows omphalocele (a) and ambiguous genitalia (b)



Photograph no 2 shows sonography of uterus(a) and testis(b)



Photograph no 3 shows karyotyping, 46, XY, add 5p(15.3)

## 5. Discussion

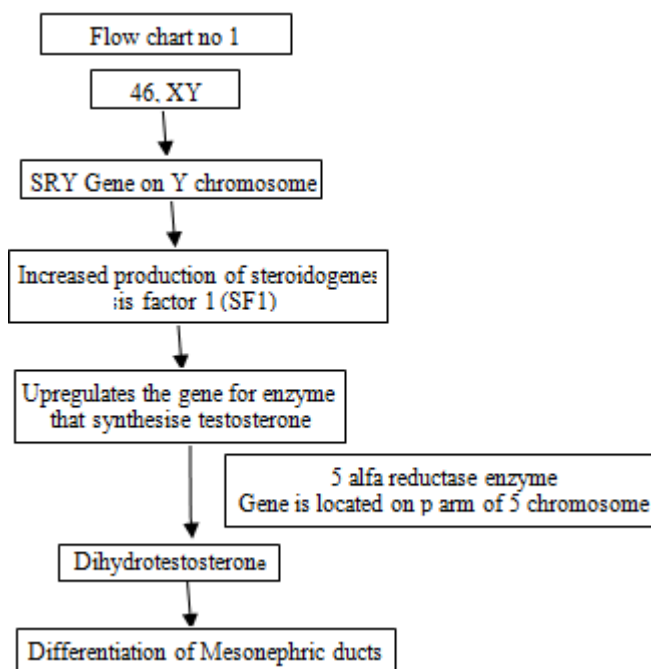
The term ambiguous genitalia is used to describe an individual's genitalia which cannot be determined by general appearance. In present case unique combination of ambiguous genitalia, omphalocele and extra genetic material on p arm of 5 chromosome is observed. Embryological and genetic basis of this unique combination is discussed.

Omphalocele or exomphalos is an abdominal body-wall defect in which bowel and or liver protrudes into the umbilical cord. Failure of returning of organs to abdominal cavity leads to omphalocele. The eviscerated organs are enclosed by a membrane consisting of peritoneum and amnion. Associated anomalies and abnormal karyotypes occur frequently<sup>3</sup>. The most frequent chromosomal anomalies associated with omphalocele are trisomy 13, 18, 21 and Beckwith Wiedemann syndrome<sup>4,5</sup>. Cardiac defects are most frequently reported anomaly in association with omphalocele<sup>6</sup>. The etiology of omphalocele is believed to be a folding defect<sup>6,7</sup>. Failure of returning of organs to abdominal cavity leads to omphalocele. The process is complex however the timing of the folding process seems to play an essential role<sup>3</sup>. Isolated omphalocele were more likely to have a normal karyotype, however fetuses with multiple anomalies were more likely to have abnormal karyotype<sup>8</sup>. In the current study, we have observed omphalocele associated with abnormal karyotype i.e. 46, XY, add 5p(15.3).

In the present study, prepubertal status of uterus is noted, 1.7 x 0.8 x 0.4 cm. Bilateral ovaries poorly delineated, two well defined echogenic structures are noted each in the bilateral inguinal areas at lower end with evidence of internal vascularity likely testis. Genital tubercle is seen which formed the clitoris and absence of penis is noticed. Along with this 17-OH progesterone is mildly raised (3.7ng/ml). This mildly raised 17-OH progesterone may be the reason for ambiguous genitalia.

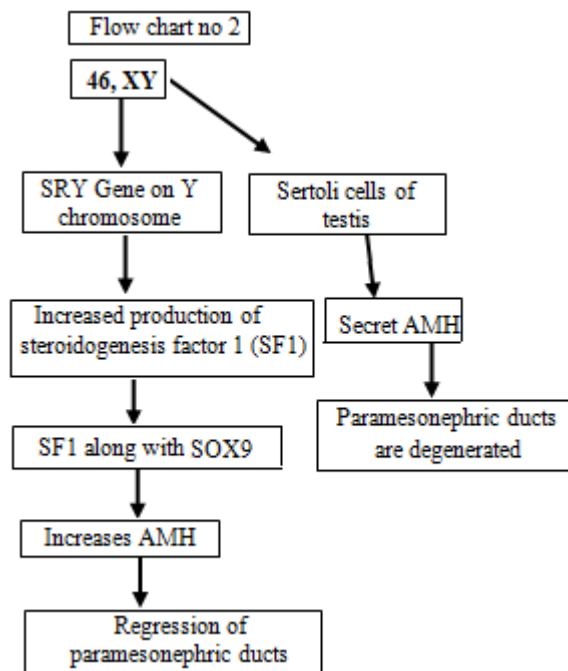
Testis, ovaries and uterus is present in the present study of child who has 46, XY, add + 5p (15.3) chromosomal constitution. This shows that there is development of mesonephric and paramesonephric ducts. Y chromosome has SRY gene which causes production of steroidogenesis factor 1 (SF1)<sup>9</sup>. This factor upregulates the gene for enzyme that synthesise testosterone. Testosterone is converted into more potent androgen dihydrotestosterone by enzyme 5 alpha reductase enzyme, the gene (SRD5A1) for it is located on p arm of 5 chromosome<sup>10</sup>. We have found additional genetic

material on p arm of 5 chromosome whose origin is unknown. To get added extra genetic material, break in the p arm of 5 chromosome at 15.3 band would have occurred. During the process of breakage, the SRD5A1 gene would have got deleted and so 5 alpha reductase enzyme would have not produced. Conversion of testosterone into dihydrotestosterone might have not occurred and so differentiation of mesonephric duct would have failed. 17-OH progesterone is mildly raised which is converted into androstenedione and then into testosterone. This could be explanation for partial development of mesonephric ducts (Flow chart no 1).



On the other side paramesonephric ducts are developed to form uterus (Flow chart no 2). Steroidogenesis factor 1 (SF1) produced because of functioning of SRY gene on Y chromosome increases anti Mullerian hormone (AMH) along with SOX 9 gene. AMH will cause regression of paramesonephric ducts<sup>8</sup>. In the present case either down regulation of SRY gene to produce SF1 and or down regulation of SOX9 gene would cause less or no AMH which would cause no regression of paramesonephric ducts. Sertoli cells in testis secrete AMH normally which could be less because of presence of very less number of Sertoli cells.

Thus, the partial development of mesonephric ducts and paramesonephric ducts give rise to the picture of ambiguous genitalia.



Partial androgen insensitivity syndrome results into variable degrees of Wolffian duct development and external genitalia ambiguity<sup>11</sup>. Ambiguous genitalia can be associated with syndromes of multiple congenital malformations<sup>12</sup>. These associations are due to the fact that many transcription factors involved in sex development and differentiation are also involved in other developmental functions<sup>11</sup>. We have also found cardiovascular system and gastrointestinal system involved along with ambiguous genitalia. The testicular development will dictate the degree of masculinization of external genitalia, extent of Wolffian duct development and Mullerian duct regression in affected newborns<sup>11</sup>. The risk of germ cell tumour in such cases where ovotesties are present is 3%<sup>13</sup>.

Karyotype plays major role to identify the sex of the child and on that basis further mode of treatment can be planned. The presence of omphalocele on prenatal sonogram should alert the clinician of increased risk for fetal aneuploidy<sup>9</sup>. Proper genetic counselling to undergo invasive method should be offered to do fetal karyotype.

Data regarding omphalocele with abnormal karyotype is available but combination of omphalocele, ambiguous genitalia and additional genetic material on p arm of 5 number chromosome is rare.

## 6. Conclusion

Karyotype is gold standard technique in ambiguous genitalia to find out the sex of child. Prenatal diagnosis should be if omphalocele was observed on prenatal scan.

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