A CASE REPORT - JACOB SYNDROME (45X/47XXY MOSAICISM)

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ABSTRACT

Objective: XYY syndrome is a rare chromosomal aneuploidy that affects males with an incidence of 1 in 1000. Males with this syndrome typically appear normal and have normal sexual responsiveness and fertility. However, they may be taller than average and have a variable risk of cognitive and behavioral deficits. Herein, we report a rare case of XYY aneuploidy presenting with ambiguous genitalia which was initially treated as congenital adrenal hyperplasia.

A 7-month-old infant was referred by a pediatrician to the Endocrine Out-patients' department with complaints of ambiguous genitalia by his parents and undescended testes after taking the consent detailed history was taken and a previous medical record was reviewed followed by a detailed examination done. As the suspicion of the chromosomal defect was raised, the patient was advised to do karyotyping. The karyotyping counted 30 cells: 21 cells showed 45 while 09 cells showed 47 chromosomes. thus, the diagnosis of Jacobs syndrome was made and confirmed. Most cases of 47XYY syndrome are not inherited but arise as a random event, mostly by paternal disjunction at meiosis II. However, most patients live a normal life, only requiring conservative management of their behavioral deficits.

Keywords: 47XYY, Chromosomes abnormality, Karyotyping, Aneuploidy, Non-disjunction

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INTRODUCTION

Chromosomes are cells' structures containing DNA and many genes. There are 23 pairs of chromosomes in each cell in the human body, with 22 pairs known as autosomes and one pair determining sex as sex chromosomes. In a male, this typically includes one X chromosome and one Y chromosome (XY). XYY syndrome or Jacobs syndrome is a rare genetic condition that occurs when a male has an extra copy of Y chromosomes in each of their cells (XYY).

Jacob syndrome, also known as 47 XYY syndrome, is a rare genetic condition that occurs in about 1 out of 1000 male babies. It comes under "sex chromosome trisomies". The discovery of the condition dates back to the 1960s.[1] Parental nondisjunction at meiosis II results in an extra Y chromosome, producing a 47 XYY karyotype in the affected offspring. 46XY/47XYY mosaics from parental nondisjunction during cell division after post-zygotic meiosis can result in the addition of the extra Y chromosome in early embryonic development.[2]

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The median age of diagnosis of Jacob syndrome is approximately 17 years. Many patients present with infertility concerns in adulthood. Patients' presentation varies greatly, with a few patients having phenotypic concerns, including macroorchidism, tall stature, macrocephaly, and hypertelorism. Moreover, conditions like asthma, autism spectrum disorders, and seizures prevail more in such patients.[1] Although 1 in 1000 boys have the karyotype 47XYY, there is a paucity of information about the phenotype, and approximately 85% or more of males with XYY are never diagnosed.[4]

In hypospadias, karyotypes are normal in most cases. However, many types of chromosomal abnormalities in hypospadias have been reported in the literature: 47 chromosomes with XXY sex complement.[7]

Here, we report one rare case of Jacob syndrome with 45X/47XYY mosaicism with ambiguous genitalia with hypospadias in a 7-month-old infant.

Case history A 7-month-old infant was referred by a pediatrician to Endocrine OPD with a complaint of ambiguous genitalia and left undescended testis. Detailed history revealed that the child was born as a result of non-consanguineous marriage, at 35 weeks of gestation in a public sector health institute through spontaneous vaginal delivery with a birth weight of 3kg and an APGAR score of 9. The pregnancy was complicated due to delayed fertility for 3 years and the use of herbal medicines by the mother. Paternal age was 23 and maternal age was 21 years at the time of conception.

The general physical appearance of the baby was normal with his height at the 50th centile and weight below the 5th centile in the CDC chart. Examination of genitalia shows penoscrotal hypospadias (grade 3) and cryptorchidism. There was no clinodactyly, hypotonia, hypertelorism, asthma, and seizure disorder.

At 1 month's age, Ultrasound showed hydrocoele and serology showed a serum 17-OH- progesterone level of 7.30 (0.07-0.7) with normal serum electrolytes. Inguinal scrotal ultrasound shows left undescended testes with inguinal hernia. He was started on cortisol 2mg and fludrocortisone for a presumptive diagnosis of congenital adrenal hyperplasia. Then Karyotyping was advised which showed "45X [21]/47XYY [09], 30 cells were counted; 21 cells showed 45 while 09 cells showed 47 chromosomes, showing a mosaic pattern. (Fig 01)

The diagnosis of Jacob syndrome was made and confirmed upon karyotyping, after that cortisol and fludrocortisone were stopped, and serum 17-OH- progesterone was repeated which was reported as <0.03 (0.03-0.90) with normal serum electrolytes.

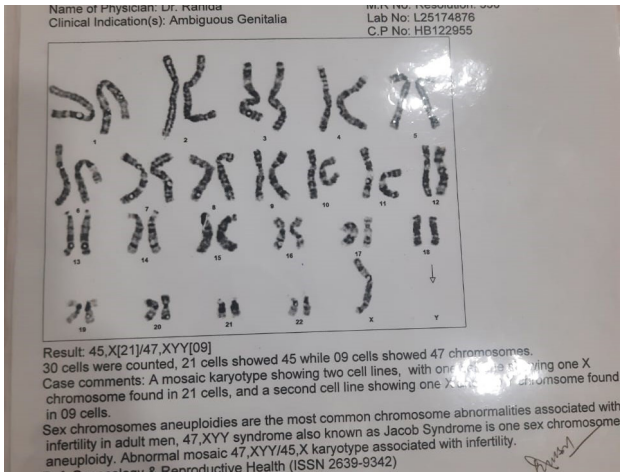

Fig 1: Karyotyping report

DISCUSSION

Jacob syndrome, also known as 47 XYY syndrome occurs in about 1 out of 1000 male children.[1] Diagnosis is often delayed, with the average age of diagnosis being approximately 17 years.[3] Jacob syndrome commonly arises during meiosis II in the father during which an extra Y chromosome is attributed to the resultant sperm. Another form of this condition 46XY/47XYY arises during early embryonic development.[2] Disease symptoms might be quite vague during childhood, however, men with Jacobs syndrome exhibit hypotonia, macrocephaly, tall stature, clinodactyly, and hypertelorism. [2]

Probing into the history of a patient with Jacobs syndrome may reveal mild learning disabilities and behavioral disturbances as patients may have had delayed speech onset as children, attention deficit hyperactivity disorder (ADHD), and autism spectrum disorder (ASD). Moreover, asthma, seizure disorder, and tremors are also common. Males in adulthood may present with a history of infertility and/or decreased libido. Atrophic testicles may be observed. In addition to this, about half of the patients may manifest flat feet and dental abnormalities such as underbites and macrodontia.[4]

Diagnosis of Jacobs syndrome may occur in the early prenatal period by a technique known as non-invasive prenatal testing using cell-free fetal DNA which has high accuracy for detecting sex chromosomes aneuploidy. Amniocentesis is a more invasive method of prenatal diagnosis but is not in use anymore.[5] After the birth, diagnosis is made using karyotype analysis from the patient's blood sample. 47XYY males who are being seen for infertility should undergo semen analysis, testicular ultrasound, and blood work to measure levels of reproductive hormones.

Families who receive prenatal diagnosis should receive genetic counseling to help them understand the disease. The treatment of this syndrome is supportive and involves behavioral and speech modification and appropriate medical treatment for any co-morbid conditions such as asthma and seizures. Men with infertility should undergo comprehensive evaluation from a qualified reproductive endocrinologist.

According to studies, patients with Jacob syndrome live 10 years less than their age-matched peers who do not have the disease. [2] But many men with Jacob syndrome go on to live a normal life.

CONCLUSION

XYY syndrome patients very often live nearly normal lives with the condition. Patients should be reassured and counseled. The fact that up to 85% of these cases go undiagnosed is a testament to the mild symptoms but our patients presented at such a young age with ambiguous genitalia and hypospadias. Patients should also be educated regarding their fertility status and future reproductivity. Management of this disease requires collaboration and effective communication with the patient's interprofessional team. Karyotyping is important in the workup of ambiguous genitalia and hypospadias as it guides toward proper diagnosis and management.

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