BJMG 24 (2), 2021 • 103-106
DOI: 10.2478/bjmg-2021-0029
sciendo

CASE REPORT

48,XYYY: A RARE CASE REPORT

Sabnis AS[1,*], Bhusare D[2]

[*]**Corresponding Author:** Dr. Anjali S Sabnis, M.D. Professor and head, Department of Anatomy, MGM Medical College and Hospital, Kamothe, Navi Mumbai - 410209. India, Mobile no: 9820493036, email address: dranjus2003@yahoo.com

ABSTRACT

A case study of a 4 year old child with hypospadias and cryptorchidism on the right side is presented. Combined analysis by Karyotype and FISH showed a mosaic pattern of 48, XYYY (73%); 47,XYY (7%); 46,XY (7%) and 45,X (13%). Apart from hypospadias and cryptorchidism there were no significant phenotypic changes observed. Inheritance of this clonal abnormality was ruled out as the karyotype patterns of the child's father and brother both showed a normal karyotype. For further management, genetic counseling, and the correction of hypospadias and the undescended testis were recommended .

Key words: Y chromosome; Supernumerary Y chromosome; Modified Klinefelter syndrome

INTRODUCTION

Gain or loss of chromosome leading to an abnormal number of chromosomes is termed as aneuploidy. Aneuploidies are chromosomal abnormalities that represent the change in the number of chromosomes, either in trisomy or monosomy forms, both in autosomes and sex chromosomes X and Y. An alteration in genetic dosage in sex chromosome aneuploidy may lead to neurological deficits and congenital anomalies of the reproductive system. Deletion or presence of an extra X or Y chromosome leads to monosomy and supernumerary chromosomes respectively. Different polysomy conditions like 47,XXY; 47,XYY; 47,XXX; 48,XXYY and monosomy conditions like 45,X (Turner syndrome) are seen with an abnormal number of sex chromosomes. 47,XXY is the most common sex chromosomal aneuploidy with a prevalence of one in 500 males [1]. The 47,XYY condition is the next common sex chromosomal abnormality after Klinefelter syndrome [2]. 48,XYYY is a rare condition where the presence of two extra supernumerary Y chromosomes alters the genetic dosage. Up until now, very few cases of XYYY have been reported across the world, with wide variety of clinical features. In the present case, a 4 year old boy was genetically investigated in order to find an association with hypospadias with undescended testis. The karyotype analysis revealed 48,XYYY without mosaics, which was confirmed by FISH with mosaicism, 48,XYYY (73%); 47,XYY (7%); 46,XY(7%) and 45,X(13%). Associated with 48,XYYY are phenotypic changes in neurological development, reproductive system development, and skeletal system development leading to mental retardation, small testes, cryptorchidism, lack of sexual desire, dysmorphic features and behavior disturbances. These occur because of the extra gene dosage mechanism .

The present case is discussed in detail for clinical and combined karyotyping and FISH investigations in order to study the association with hypospadias along with undescended testis.

CASE REPORT

A 4 year old male child with hypospadias with cryptorchidism on the right side presented to the MGM hospital, Navi Mumbai on the 11TH of June 2017. There was an absence of dysmorphism or any other phenotypic changes. [Figure 1] Upon examination of the left testis, it was observed that the scrotal sac appeared normal in size, shape and echo texture on ultrasonography with post orchidopexy changes . The right testis was not visualized in the scrotal sac nor in inguinal region. This was confirmed by MRI scanning. To further investigate any association between chromosomal aberration and congenital anomalies, the patient was referred to the cytogenetic laboratory in the Department of Anatomy. Cytogenetic analysis for conventional karyotyping was done by 72 hours culturing,

[1] Department of Anatomy, MGM Medical College and Hospital, Kamothe, Navi Mumbai, India

[2] Department of Pediatric Surgery, MGM Medical College and Hospital, Kamothe, Navi Mumbai, India

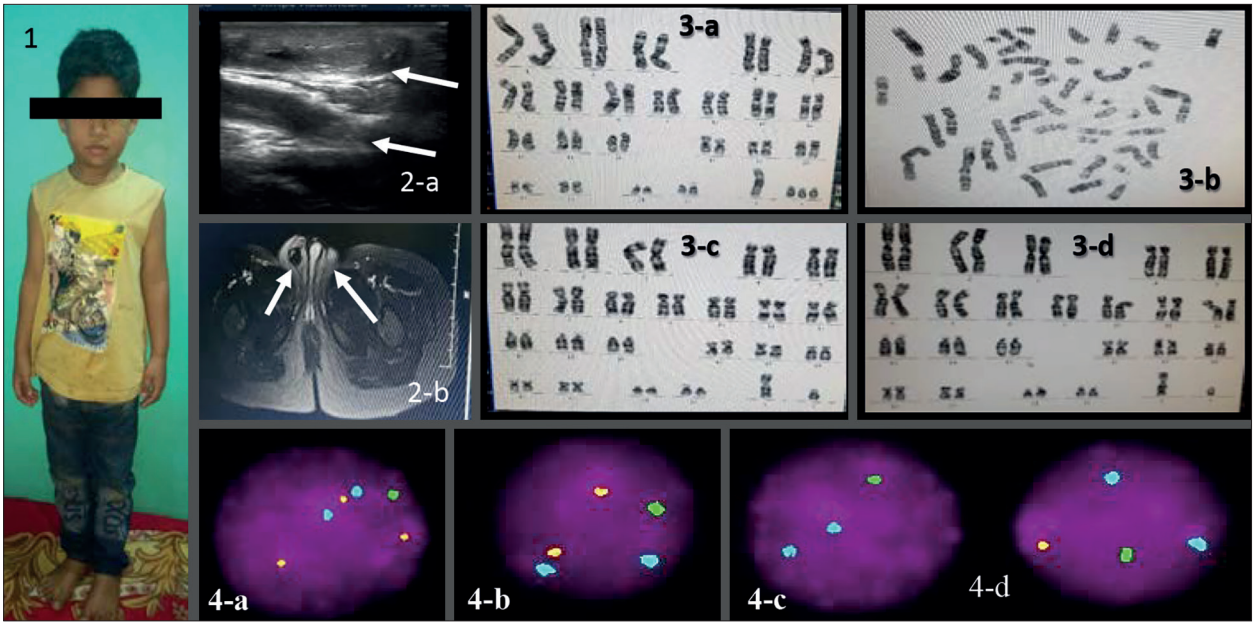

Figure 1. (1)- phenotype of proband. (2-a) ultrasonography (2-b) MRI shows absence of right testis and presence of right testis (arrow). (3-a) shows karyotype of proband, (3-b) shows metaphase spread of proband, (3-c, 3-d) shows karyotype of father and brother of proband. (4-a-d) shows FISH analysis. Green, orange, aqua signal shows X, Y & 18 chromosome respectively. (4-a)-XYYY pattern (73% cells), (4-b)-XYY pattern (7% cells), (4-c)- 1 X chromosome in each cell (13%), (4-d)- XY pattern in 7%.

harvesting and the GTG-Banding method [3]. Imaging was done by using Metasystem software and a Carl Zeiss microscope. 50 complete and well spread metaphases were selected for reporting. Analysis revealed the presence of two extra Y chromosomes in 50 metaphase cells. By using the microscope Axioimager Z2 from Zeiss, Metasystem ISIS software and a Vysis CEP probe for X (green signal) Y (orange signal) and 18 (aqua signal), Fluorescence in situ hybridization (FISH) analysis was done at Jaslok Hospital, Mumbai to investigate chromosomal pattern. Analysis showed a mosaic karyotype with the presence of four cell lines 48,XYYY (73%); 47,XYY (7%); 46,XY(7%) and 45,X(13%) in a mosaic pattern. In order to rule out the role of inheritance, the patient's father and brother were advised to do karyotyping as well. This showed normal male chromosomal patterns. 48,XYYY is a rare sex chromosomal numerical abnormality, for which genetic counselling is strongly recommended.

DISCUSSION

The present case is of a 4 year old male child with hypospadias and cryptorchidism on right side, showing two extra Y chromosomes. The presence of supernumerary Y chromosomes is a rare phenomenon. The mechanism by which a patient gets two extra Y chromosomes is not clear. The most likely explanation appears to be one originally proposed by Townes et al. that non-disjunction in spermatogonia mitosis followed by 2nd non-disjunction of one Y chromosome in meiosis would result in the formation of sperm bearing three Y chromosomes [4]. Sperm containing three Y chromosomes could theoretically be produced by secondary non-disjunction or anaphase lagging in meiosis II from a XYY primary spermatocyte [5]. Fertilization of normal ovum by YYY sperm would probably give rise to the XYYY condition. In the present case, cytogenetic analysis of the peripheral blood of the father of the child showed a normal male chromosomal pattern, indicating the absence of inheritance for the XYY karyotype in the present case.

The XYYY pattern is mostly observed with a mosaic pattern of XYY, XY and/or X, [6-18] and can also be seen as a single clone. Out of 15 cases, a mosaic pattern is seen in 7 cases, and pure XYYY is seen in 8 cases (Tables 1 and 2). The range of age in which pure XYYY and mosaic pattern appears is from 13th week to 53 years. Individuals with XYYY have widely varying phenotypes with regard not only to physical signs but also to brain functions and cognitive performance [19]. XYYY is associated with clinical features like bossy behavior, argumentative, loud voiced, friendless [4], frequent respiratory infections, inguinal hernia, hypoplastic middle phalanges with a single palmar crease [4]. In one of the cases, emotional and educational difficulties were noted along with myopia at the age of 5. Behavioral changes such as aggressiveness, violence and uncontrollable acts were observed. These deteriorated gradually [20]. Adult males with 48,XYYY are tall , having incurved little fingers of both hands, small testes with a lack of sexual desire, testicular biopsy with atrophic semi-

Table 1. shows details of pure XYYY

Year	Author name	Condition	Age	Clinical features
1965	Townes PL[6]	48,XYYY	5	Recurrent respiratory infection. Inguinal hernia, right ventricular hypertrophy, pulmonary stenosis
1972	Schoepfllin G S [4]	48,XYYY	9	Aggressiveness, impulsiveness, uncurved little finger of both hands
1973	Hunter H[5]	48,XYYY	53	Boastful, friendless, loud voiced, argumentativeness
1988	Hori N[10]	48,XYYY	Adult	Lack of sexual desire, tall, incurved little finger on both hands, small testes
1992	Mazauric Stuker[12]	48,XYYY	33	Grand mal epilepsy, hollow feet and onychocryptosis of the toes, spinal ataxia of the right side, radioulnar synostosis of the left elbow, and reduced mental capacity.
1994	Stein A[14]	48,XYYY	19	Dysmorphism, MR, Problem in psychological functioning
2002	Venkataraman G[17]	48,XYYY	13 wk fetus	Post ICSI pregnancy
2018	Maryam Abedi [18]	48,XYYY	32	teeth dysmorphology, history of respiratory disease, low total body hair, long length of fingers and toes, partial deformity of the joints and nails,

Table 2. shows details of mosaic pattern of XYYY

Year	Author name	Condition	Age of patient	Clinical features
1967	D Cox[7]	Mos 45,X/ 48,XYYY	4	Pseudo hermaphrodite, Cryptorchidism on left side, uterus with blindly ending fallopian tube
1993	Teyssier M [13]	Mos 46,XY/48,XYYY	37	Obese, dysplasia of right hip, MR, aggressiveness
1995	James C [15]	Mos46, XY/47,XYY/48,XYYY	3	Bilateral radioulnar synostosis, minor facial anomalies and mild intellectual delay.
2002	Fox JE[16]	Mos45,X/46,XY/48,XYYY	infant	Ambiguous genitalia, minor ear and eye anomalies and coarctation of the aorta with bicuspid aortic valve, bilateral fallopian tubes and a left infantile testis with epididymis.
2020	Present case	48,XYYY FISH- mosaic XYYY-73%, XYY-7% X-13%, XY 7%	4	Hypospadias And Cryptorchidism On Right Side, Aggressiveness

niferous tubules without spermatogenesis [10]. A 32 year old male with 48,XYYY showed semi-Klinefelter characteristics such as a tall stature, teeth dysmorphology, long length of fingers, and partial deformity of the joints [18]. A 19 year old male with 48,XYYY showed dysmorphic features, mental retardation, and abnormal psychosocial functioning [19]. A 5 year old boy with 48,XYYY showed a mosaic pattern 45XO/48,XYYY with hypospadias but showed normal intelligence [7]. A 37 year old obese man with dysplasia of right hip, mental retardation, behavior disturbances, aggressiveness, sexual impulsions and fibrohyalination in the testis showed a mosaic pattern of 46,XY/48,XYYY [13]. A 32 year old male patient with complaint of infertility showed clinical features of long length of fingers and toes, partial deformity of joints and nails, mental health problems, teeth dysmorphology and a karyotype analysis revealed 48,XYYY [21]. 48,XYYY was observed in a fetus after intra cytoplasmic sperm injection (ICSI) [17] and a mosaic pattern of two cell lines 45,X/48,XYYY was observed in the amniotic fluid culture of an 18 week old fetus [22]. Occasional aggressive outbursts and poor emotional stability seem to be fairly consistent among 48,XYYY males [10].

In the present case, the 4 year old child showed normal phenotypic features with a height 113 cm and weighing in at 17 kg. The child maintains a good intellectual status, as shown by his school performance but shows an aggressive nature. There was an absence of dental abnormalities and other clinical features except hypospadias and cryptorchidism. The proband was born via a third degree consanguineous marriage and has one brother which is phenotypically and genotypically normal. The karyotype of lymphocytes show 48,XYYY and a FISH analysis shows a mosaic pattern of four different cell lines. 7% of the cells show a normal chromosomal pattern while 73% of the cells show 48,XYYY. 7% of the cells show 47,XYY and 13% of the cells show a 45,X pattern. The ratio of aneuploid cells to euploid cells decides the consequence of a mosaic pattern. The more aneuploid cells there are, the more abnormal the clinical features. This includes the result that the euploid cells are fewer in number, as one of the abnormal clinical features. In the present case,

93% of the cells are aneuploid cells, while 7% of the cells are euploid cells. The clinical features of hypospadias, cryptorchidism, and aggressiveness may be related to the supernumerary Y chromosome. Only one case of XYYY is reported in a fetus and the case of 4 years old male child reported is the first live case with XYYY in India .

Genetic counselling of the adult patient and the parents (in case of pediatric age) is strongly recommended. The follow up of the pediatric group of patients will be helpful to study their psychological, sexual, and personality development, thus adding to the understanding of phenotypic features and its relation to presence of triple Y chromosome .

Acknowledgment: Authors acknowledge Dr. Arundhati Athalye and Mr. Rupesh Sanap from Jaslok Hospital for carrying out FISH procedure and doing analysis.

The authors alone are responsible for the content and writing of this article

Declaration of Interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

REFERENCES

1. Visootsak J, Graham JM. Klinefelter syndrome and other sex chromosomal aneuploidies. Jr Orphanet J Rare Dis. 2006; 1: 42.
2. Gekas J, Thepot F, Turleau C, Siffroi JP, Dadoune JP, Briault S, Rio M, Bourouillou G, Carré-Pigeon F, Wasels R, Benzacken B. Chromosomal factors of infertility in candidate couples for ICSI: an equal risk of constitutional aberrations in women and men. Association des Cytogeneticiens de Langue Francaise. Hum Reprod. 2001; 16(1): 82-90.
3. Barch MJ, Knutsen T, Spurbeck JL. The AGT Cytogenetics Laboratory Manual, 3rd Edition, Lippincott- Raven, Philadelphia. 1997, Peripheral blood cytogenetic methods, 77- 87.
4. Schoepfllin GS, Centerwall WR, 48,XYYY: A new syndrome. Journal of medical Genetics. 1972; 9(3): 356-360.
5. Hunter H, Quaife R. A 48,XYYY male: A somatic and psychiatric description. J Med Genet. 1973; 10(1):80-83.
6. Townes P, Ziegler N, Lenhard L. A patient with 48 chromosomes (XYYY). The Lancet. 1965; 285: 1041-1043.
7. Cox D., and Berry C. A patient with 45XO-48XYYY mosaicism. J. Med. Genet. 1967; 4: 132.
8. Sele B., Bachelot Y, Richard J, Muller J, Jalbert P, and Berthet J. 48,XYYY males. Apropos of a case of 46,XX/47,XYY/48,XYYY mosaicism. Pediatrie. 1975; 30: 601.
9. Gigliani F, Gabellini P, Marcucci L, Petrinelli P, Antonelli A. Peculiar mosaicism 47,XYY/48,XYYY/49,XYYYY in man. Journal de Genetique Humaine. 1980; 28: 47.
10. Hori N, Kato T, Sugimura Y, Tajima K, Tochigi H, Kawamura J. A male subject with 3 Y chromosomes (48,XYYY): a case report. The Journal of Urology. 1988; 139: 1059-1061.
11. Bryke CR, Mahoney MJ, Yang-Feng TL. Antenatal diagnosis of 45,X/48,XYYY. Am. J. Med. Genet. 1989; A 34: 207-210.
12. Mazauric-Stüker M, Kordt G, Brodersen D. Y aneuploidy: a further case of a male patient with a 48,XYYY karyotype and literature review. Ann. Genet. 1991; 35: 237-40.
13. Teyssier M, Pousset G. 46,XY/48,XYYY mosaicism case report and review of the literature. Genetic Counseling (Geneva, Switzerland). 1993; 5: 357-361.
14. Stein A, Heilbronner H, Jungmann J. Sex chromosome aberration with the 48,XYYY karyotype. A case report of the phenotype of a rare sex chromosome aneuploidy. Zeitschrift für Kinder-und Jugendpsychiatrie. 1994; 22: 130-134.
15. James C, Robson L, Jackson J, Smith A. 46,XY/47,XYY/48,XYYY karyotype in a 3-year-old boy ascertained because of radioulnar synostosis. Am. J. Med. Genet. 1995; A 56: 389-392.
16. Fox JE, Blumenthal D, Brock W, Kreitzer P, Cooper R, Anderson D, *et al*. Infant with mos45,X/46, XY/47, XYY/48, XYYY: Genetic and clinical findings. Am. J. Med. Genet. 1995; A 59:435-440.
17. Venkataraman G, Craft I. Triple-Y syndrome following ICSI treatment in a couple with normal chromosomes Case report. Hum. Reprod. 2002; 17: 2560-2563.
18. Arash Salmaninejad M and Sakhinia E. Rare 48,XYYY syndrome: case report and review of the literature Clin Case Rep. 2018; 6 (1): 179-184.
19. Z Kinder Jugendpsychiatr. Sex chromosome aberration with 48XYYY Karyotype: A case report of the phenotype of a rare sex chromosome aneuploidy, Case reports. 1994; 22(2): 130-4
20. Ridler MAC. An adult male with XYYY sex chromosomes. Clinical Genetics. 1973; 4(1): 69-77.
21. Abedi M. Rare 48,XYYY syndrome: case report and review of the literature, clinical case reports. 2018; 6(1): 179-184.
22. Christin R. Antenatal diagnosis of 45,X/ 48,XYYY. American journal of medical genetics. 1989; 34: 207-210 .