



Distinctively Different Phenotypes of Two Cases with a Rare Karyotype of 45,X/47,XYY Mosaicism: Case Report and Literature Review

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ABSTRACT

The 45,X/47,XYY mosaicism is an extremely rare genetic disorder with highly phenotypic manifestations such as ovotesticular disorders of sexual development, mixed gonadal dysgenesis and Turner syndrome. Herein, we report two cases with very distinctive phenotypes despite having the same sex chromosome mosaicism of 45,X/47,XYY. It should be kept in mind that the rare type of sex chromosome mosaicism of 45,X/47,XYY may present with genital phenotypes ranging from normal female to male characteristics.

Keywords: 45,X/47,XYY, Turner syndrome, ambiguous genitalia, gonadal dysgenesis

Introduction

The 45,X/47,XYY mosaicism is a rare chromosomal anomaly resulting from postzygotic mitotic non-disjunction. The 45,X/47,XYY karyotype is a rare cause of disorders of sexual development (DSD) and presents with highly variable phenotypic features (1). Short stature has been reported in most of the cases with/without Turner stigmata such as webbed neck, horseshoe kidney and cubitus valgus (2). The characteristic features of this disorder remain unclear because of its low incidence (1). We aimed to present two cases with distinctly different phenotypes from each other despite having the same sex chromosome mosaicism of 45,X/47,XYY.

Case Report

Case 1

A male aged 14 years and 4 months presented to our outpatient clinic due to short stature and hypospadias. He was born as the first child of healthy non-consanguineous parents and delivered at term by normal vaginal delivery after an uneventful pregnancy. His family history was unremarkable. His past medical history revealed that he had been operated on two times for penoscrotal hypospadias when he was one and five years old. In the second session, gonadectomy was performed for atrophic left testis and he lost this during follow-up thereafter.

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On physical examination at presentation, his weight was 41 kg [-1.49 standard deviation score (SDS)], and his height was 150.3 cm (-1.93 SDS). His Tanner staging was axillary hair (+), pubic hair stage 3 and the right testis was palpable with a volume of 12 mL in the scrotum. However, the left testis was not palpable in the scrotum or inguinal region. The stretched penile length was 7.2 cm and proximal penile hypospadias was observed. Other systemic physical examination features were unremarkable. No Turner's stigmata were visualized.

The test results of his hormonal evaluation were as follows; follicle stimulating hormone (FSH): 9.37 mIU/mL (N, 1.2-10.3), luteinizing hormone (LH): 1.16 mIU/mL (N, 0.2-5), testosterone: 162.25 ng/dL (N, 100-1,200), AMH: 2.16 ng/mL (N, 2-30.7 ng/mL), adrenocorticotropic hormone: 32 pg/mL (N, 7-6,999) and cortisol: 11.6 µg/dL (N, 2-25). Mid-parental height was 164 cm (-1.98 SDS) and bone age was consistent with his chronological age. On hormonal examination for short stature, insulin-like growth factor-1 was 260 ng/mL (-1 SDS), insulin-like growth factor binding protein-3 was 6,270 ng/mL (+0.18 SDS) while peak growth hormone release with L-dopa was within normal limits (15.5 ng/mL). Ultrasonographic examination of the scrotum revealed that the right testis was in scrotum. However, the left testis was not seen in the scrotum, inguinal or pelvic region and also no Mullerian structure was detected on pelvic ultrasonography. Chromosome analysis from peripheral blood cells revealed the presence of 45,X/47,XYY mosaicism (46-44, respectively) (Figure 1). The case was discussed in DSD council and hypospadias repair was performed. On his last physical examination when he was 17 years and 10 months of age, his weight was 51.5

kg (-2.4 SDS), his height was 156 cm (-3.1 SDS), his body mass index was 20.9 kg/m² (-0.7 SDS), the right testis was palpable as 20 mL in the scrotum, the left testis was non-palpable, pubic hair development was Tanner stage 5, and stretched penis length was 10.4 cm. Laboratory examination showed FSH: 19.3 mIU/mL (1.2-10.3 mIU/mL), LH: 11.1 mIU/mL (0.2-5 mIU/mL), and total testosterone: 716 ng/dL. He described normal erection and ejaculation. Spermogram analysis revealed 1.2 million/mL sperm, which suggests insufficiency and therefore Kruger assessment could not be carried out. He was monitored for tumour markers including Alpha-Fetoprotein and beta-human chorionic gonadotropin and testicular ultrasound for the probable development of gonadal tumours and fortunately, no evidence of gonadal tumour had been detected at the time of writing. Chromosome analyses of the parents were unremarkable. Written informed consent was obtained from the patient and his parents for the publication of this case report and any accompanying images.

Case 2

A female aged 16 years and 9 months presented to our outpatient clinic for primary amenorrhea. She was the first child of non-consanguineous parents and delivered at term (40-weeks) by normal vaginal delivery with a weight of 2,100 gr. Her family history was unremarkable, but pregnancy was achieved by ovarian stimulation therapy.

On physical examination, her weight was 46.8 kg (-1.67 SDS), her height was 149.6 cm (-2.23 SDS), blood pressure was 110/66 mmHg, and webbed neck, clinodactyly, low-set ears, cubitus valgus, low hairline and multiple pigmented nevus were observed. Pubertal Tanner stage was compatible with

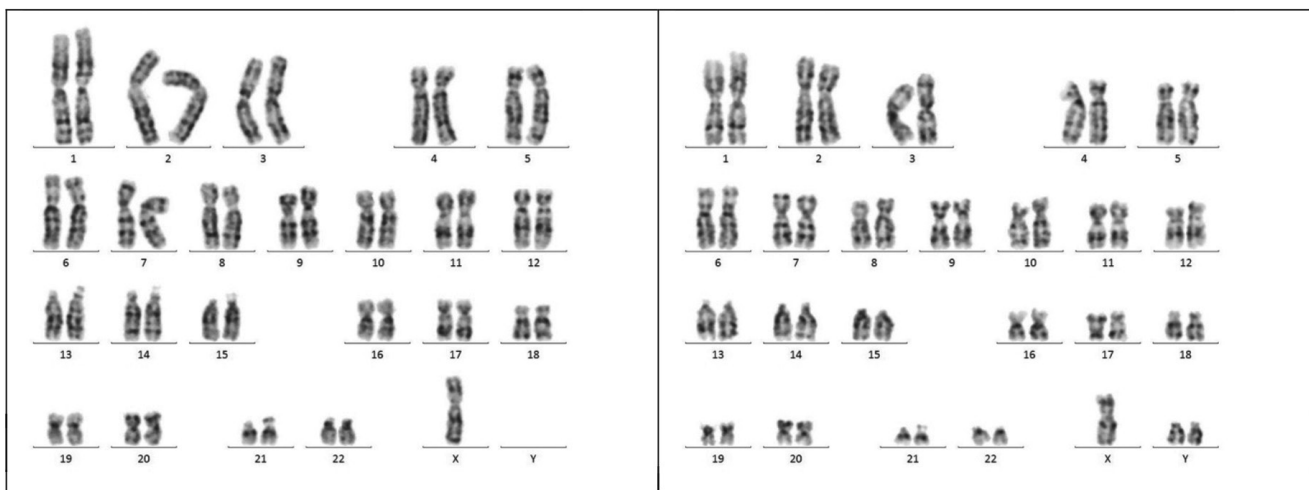


Figure 1. Karyotype of case 1

stage 1 for breast development and stage 5 for pubic hair. No enlarged clitoris or palpable gonads were visualized (Figure 2A, 2B and 2C). Mid-parental height was 167.5 cm (+0.35 SDS) and bone age was compatible with 12 years of age according to the Greulich and Pyle atlas. Initial laboratory investigations showed normal full blood count, electrolytes and renal, liver, thyroid functions. Hormone analysis revealed hypergonadotropic hypogonadism as follows; FSH: 138.4 mIU/mL LH: 29.3 mIU/mL and estradiol <10 ng/dL. Her echocardiography was normal. An ultrasonographic examination of the pelvis revealed atrophic uterus and streak gonads located in their normal positions. Chromosome analysis from peripheral blood cells revealed 45,X/47,XYY (15-35, respectively) (Figure 2D). Bilateral gonadectomy was performed and histopathological examination revealed streak gonadal structure and no evidence of malignancy. This patient, who presented with Turner syndrome phenotype, was raised as a girl and oestrogen replacement therapy was started. Growth hormone replacement therapy was not initiated due to the family's disapproval. Written informed

consent was obtained from the patient and her parent for publication of this case report and any accompanying images.

Discussion

We have reported two 45,X/47,XYY mosaicism cases showing different phenotypic features and reviewed the literature based on these cases. Chromosomal mosaicism is generally considered to be the consequence of an event occurring at an early stage of cell division. The 45,X/47,XYY mosaicism is a quite rare cause of sex chromosome DSD. Although its incidence is not clearly known, the incidence of 45,X/46, XY and 45,X/47,XYY chromosomal mosaicism is given as 1.7/10,000 and cases with the 45,X/47, XYY karyotype constitute a small part of this group (1).

Patients with 45,X/47,XYY were included in the DSD group due to sex chromosome disorder in the 2006 DSD Consensus and termed as "mixed gonadal dysgenesis" (3).

Phenotypic manifestations are highly variable in the 45,X/47,XYY karyotype. Minor or major phenotypic differences can be seen in individuals with the same mosaic karyotype. While some of the male cases have ambiguous genitalia; in some cases, fertility problems may be observed with completely normal genitalia (2). Some cases may present with Turner stigmata with female phenotype. The first case with the 45,X/47,XYY karyotype was reported in 1961 by Jacobs (4). This case had female genitalia and Turner stigmata such as short stature and webbed neck, similar to our case number 2. The underlying mechanism of the correlation between phenotype and mosaicism is not yet clear, which may be related to the very low incidence of this mosaicism (2). When all previously reported cases in the literature were reviewed, it was found that the mosaicism ratio did not affect the phenotype. Further cases are required to clarify this issue. In 1991, Pettenati et al. (5) reported on the largest series to date and focused on the clinical discrepancy of those cases diagnosed with prenatal or postnatal features. A total of 18 cases with heterogeneous phenotype having the 45,X/47,XYY karyotype have been reported to date. The median age of the previously reported cases was 11 years (interquartile range: 0-20). Four out of these 18 cases were diagnosed prenatally. Short stature was reported in 7 cases (38.9%), and the characteristics of Turner syndromes were reported in 6 (5 of them were raised as female, and the remaining one as male) patients. Five had ambiguous genitalia (2 hypospadias, 2 enlarged clitorises and one patient had small phallus, hypospadias and fused labioscrotal folds). Nine cases were raised as

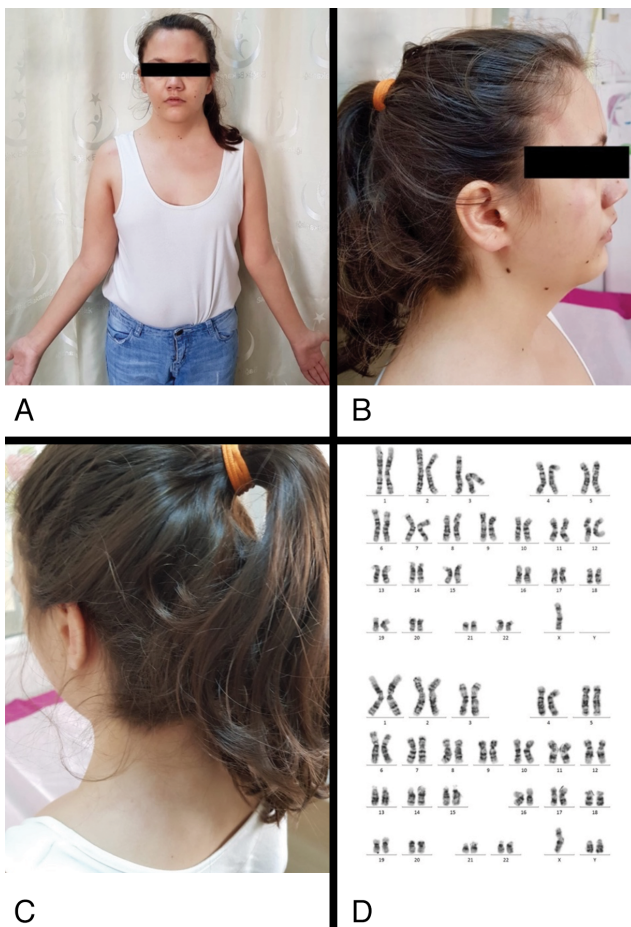


Figure 2. The phenotypic features of case 2 (A, B, C) karyotype of the case 2 (D)

female (56.3%) and 7 cases as male (43.7%). The detailed clinical and laboratory characteristics of the literature cases are presented in Table I.

The estimated risk of developing gonadoblastoma vary from 7% to 30% in female phenotype gonadal dysgenesis with 45,X mosaicism containing Y chromosome and in some studies bilateral prophylactic gonadectomy is recommended (6,7). However, in some studies, a very low incidence of gonadoblastoma development has been reported. Although prophylactic gonadectomy in the female phenotype is still controversial, it seems to be the only way to exclude malignancy (8). Prophylactic gonadectomy was applied in our case number 2, who was raised as a girl and, fortunately, no histopathological evidence suggesting gonadoblastoma was detected. It is unclear whether or not to remove the testes in phenotypic normal males. Close follow-up of the gonads with physical examination is the best prevention against the development of gonadoblastoma and dysgerminoma (5). In our first case, the atrophic testis was removed and the intact testis was preserved. In the follow-up, he was monitored for some tumour markers and testicular ultrasound for the potential development of gonadal tumours.

In 2020, Zhang et al. (9) reported pregnancy, and normal vaginal delivery resulting from in vitro fertilization using spermatozoa surgically retrieved from a male patient with 45,X/46,XY mosaicism. Similarly, in patients with male phenotype having 45,X/47,XYY chromosomal mosaicism, it may be possible to achieve fertility if the gonads are preserved.

An insufficient number of spermatozoa were observed in the semen analysis of our case raised as male, and he will be re-evaluated when fertility is planned.

Conclusion

In this study, we presented two cases of 45,X/47,XYY mosaicism with distinctly different phenotypes. Since the characteristics of this disorder remain unclear because of its low incidence, further studies are required to clarify this issue. It should be kept in mind that the rare type of sex chromosome mosaicism of 45,X/47,XYY may present with genital phenotypes having normal female or male characteristics.

Table I. Clinical characteristics of patients with 45,X/47,XXY karyotype										
Case no	Reference	Age at assessment	Clinical features	Reared gender	FSH/LH (mIU/mL)	Karyotype percent		External genitalia	Internal genitalia	Conads
						45,X %	47,XXY%			
1	Jacobs (4)	20 y	Short stature Neck webbing	F	NA	69	25	Normal female with sexual hypoplasia	No laparotomy	No laparotomy
2	Cooper et al. (10)	16 y	Short stature Shield chest Widely spaced nipples	F	NA	2	96	Normal female with sexual hypoplasia	Absent uterus Blind Fallopian tubes	Streak gonads in position of ovaries
3	Trowell and Hamilton et al. (5,11)	29 y	Short stature	M	NA	63	37	Normal male	NA	Testicular tissue; tubules lined only with Sertoli cells, well-preserved Leydig cells
4	Mulcahy et al. (11)	NB	Enlarged clitoris Bilateral inguinal hernia	F	NA	60	40	Enlarged clitoris	Normal female	Gonads attached to broad ligament; testicular tissue
5	Lisker et al. (12)	22 y	Short stature High arched palate Low-set ears Low hairline Short neck Cubitus valgus Multiple pigmented nevus	F	58/130	53	47	Normal female	Streak gonads Ovarian stroma	
6	Pettenati et al. (5)	Fetus	None	M	NA	25	75	Normal male	Normal male	
7	Pettenati et al. (5)	Fetus	None	M	NA	90	10	Normal male	No laparotomy	No laparotomy
8	Pettenati et al. (5)	6 m	No abnormalities except genitalia	F	NA	83	17	Enlarged clitoris	Infantile uterus Small Fallopian tubes and cervix Infantile vagina	Left inguinal testis Right streak gonad
9	Pettenati et al. (5)	11 y	Short stature Shield chest Low hair line Cubitus valgus Pigmented nevi	F	NA	10	90	Normal female	Partially uncanalised uterus	Streak gonads No evidence of malignancy

Table I. Continued										
Case no	Reference	Age at assessment	Clinical features	Reared gender	FSH/LH (mIU/mL)	Karyotype percent		External genitalia	Internal genitalia	Gonads
						45,X %	47,XXY%			
10	Pettenati et al. (5)	16 m	Short stature Epicanthal folds Depressed nasal bridge Systolic murmur	M	NA	18	82	Midshaft penile hypospadias	Presence of mullerian duct remnants and rudimentary vagina and uterus	NA
11	Pettenati et al. (5)	Fetus	No abnormalities except genitalia	Terminated	NA	20	80	Normal male	No Mullerian structure	Undescended testes (autopsy)
12	Pettenati et al. (5)	NB (10-day old)	High arched palate Posteriorly rotated ears Micrognathia Neck webbing Pectus excavatum	M	NA	10	90	Small phallus Severe chordee Fused labioscrotal folds Undescended testes	Uterus with left Fallopian tube, rudimentary right Fallopian tube and vagina	Immature testes
12	Fukui et al. (8)	NA	Short stature High arched palate Cubitus valgus	F	10.9/0.2 (50.2/9.0)*	12	87	Normal female	Hypoplastic uterus Normal vagina	Ovarian stroma with nests of gonadoblastoma
14	Lin et al. (13)	Fetus	Hypoplastic nasal bone Large facial angle	Terminated	NA	66	34	Normal male	NA	NA
15	Anik et al. (14)	NB	No abnormalities except genitalia	M	3.9	80	20	Hypospadias Posteriorly fused labia majora	No Mullerian structure	NA
16	Farrugia et al. (1)	NA	None	M	NA	NA	NA	NA	NA	NA
17	Farrugia et al. (1)	15 y	High arched palate Skin pigmentation Long fingers Deafness Reduced vision TAPVD	F	NA	NA	NA	NA	NA	PLAP (+) gonads
18	Farrugia et al. (1)	NA	None	F	NA	NA	NA	NA	NA	NA

Table I. Continued

Case no	Reference	Age at assessment	Clinical features	Reared gender	FSH/LH (mIU/mL)	Karyotype percent		External genitalia	Internal genitalia	Gonads
						45,X %	47,XYY%			
Present case 1		14 y	Short stature	M	9.3/1.1	46	44	Hypospadias	Undescended testes	One atrophic testis
Present case 2		16 y	Short stature Neck webbing Clinodactyly Low hair line Cubitus valgus Pigmented nevi	F	138.4/29.3	30	70	Normal female	Hypoplastic uterus	Streak gonads

*Following luteinizing hormone-releasing hormone stimulating test. Normal references of the parameters as follow: FSH: prepubertal: 0.2-11.1 mIU/mL Tanner stage 2: 1.7-4.6 mIU/mL Tanner stage 3: 2.5-7.04 mIU/mL Tanner stage 4: 1.2-7.3 mIU/mL Tanner stage 5: 1.02-9.2 mIU/mL, LH prepubertal <0.2 mIU/mL Tanner stage 2: 0.2-4.9 mIU/mL Tanner Stage 3: 0.2-5 mIU/mL Tanner stage 4-5: 0.4-7 mIU/mL.
y: Year, m: month, NB: Newborn, M: Male, F: Female, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, NA: Not available, TAPVD: Total anomalous pulmonary venous drainage, PLAP: Placental-like alkaline phosphatase

Ethics

Informed Consent: Written informed consent was obtained from the patient and his parents for the publication of this case report and any accompanying images.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.K., S.A., Ö.N., Concept: Ö.K., S.A., Beh.Ö., Design: Ö.K., S.A., Data Collection or Processing: T.K., G.A., B.Ö., Analysis or Interpretation: Ö.K., K.M.E., Y.B.K., Literature Search: Ö.K., S.A., Writing: Ö.K., S.A., K.M.E., Beh.Ö.

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