

# Sexual function and clinical features of patients with Klinefelter's syndrome with the chief complaint of male infertility

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## Summary

In this report, we present the overall sexual function and clinical features of patients with Klinefelter's syndrome with the chief complaint of male infertility. The study consisted of 40 patients with a control group of 55 infertile non-azoospermic males with a normal 46,XY karyotype who visited the Reproduction Center of Toho University Hospital during the 5.5-year period between January 1991 and June 1996 with the chief complaint of male infertility. Among the 40 patients with Klinefelter's syndrome, 38 cases were pure 47,XXY, one case was 47,XXY with a pericentric inversion of chromosome 9 and one case was a mosaic of 46,XY/47,XXY(2:28). Thirty-nine of these 40 patients were azoospermic and one (47,XXY) had severe oligoasthenozoospermia. The sexual function of the patients was evaluated according to their responses to a preliminary questionnaire devised by our department. There was no significant difference in the frequency of sexual function disturbances between the patients with Klinefelter's syndrome and the control group (67.5% vs. 60.0%;  $\chi^2$  analysis;  $p = 0.454$ ). The mean frequency of sexual intercourse per month in the patients with Klinefelter's syndrome was significantly higher than in the control group ( $4.4 \pm 2.8$  vs.  $3.3 \pm 1.6$ : Welch's  $t$ -test,  $p < 0.05$ ). A possible explanation for this variation may lie in the fact that many of these patients were diagnosed with azoospermia prior to the administration of the questionnaire and may have wished to continue to have relations as a couple.

**Keywords:** clinical features, chromosome abnormality, Klinefelter's syndrome, male infertility, sexual function

## Introduction

Klinefelter's syndrome is a frequently occurring gonadal developmental disorder that has been found in about 1 in every 1000 male infants (Maeda *et al.*, 1991). These individuals typically exhibit a 47,XXY karyotype. In 1942, Klinefelter initially reported that the disorder was associated

with atrophic testes, gynaecomastia and azoospermia (Klinefelter *et al.*, 1942). However, the mechanism by which the extra X chromosome leads to testicular dysfunction is still unclear. In patients with the chief complaint of male infertility, Klinefelter's syndrome is the most commonly found chromosome abnormality as reflected by the 11.4% incidence of Klinefelter's syndrome among azoospermic patients (Yoshida *et al.*, 1996).

Most patients with Klinefelter's syndrome are totally infertile and the results of their testicular biopsies show

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Sertoli cells only or Leydig cells only (Yoshida *et al.*, 1996). In order to conceive children, most Klinefelter's patients must rely on artificial insemination using donor spermatozoa (AID). However, we initially consider the patient's quality of life, including social and sexual aspects, before conducting AID.

In this report, we present the clinical features of patients with Klinefelter's syndrome in whom the chief complaint was of male infertility and compare their sexual function to that of non-azoospermic infertile males who exhibited a normal 46,XY karyotype.

## Materials and methods

### Patients

The subjects consisted of 40 patients with Klinefelter's syndrome and 55 non-azoospermic, infertile 46,XY males who visited the Reproduction Center of Toho University Hospital with the chief complaint of male infertility during the 5.5-year period between January 1991 and June 1996.

### Sexual function

According to a questionnaire issued by our department as shown in Table 1, the sexual function of each patient was evaluated prior to performing chromosome analysis.

### Chromosome analysis

Karyotyping was conducted by analysing G-banding using the peripheral blood lymphocyte culture technique. Fluorescent in-situ hybridization (FISH) using sex chromosome-specific DNA probes was also used in one case.

### Semen analysis

Semen analysis was performed on samples obtained by masturbation at the hospital after 5 days of sexual abstinence according to methods recommended by the World Health Organization (WHO, 1992), using a Thoma-Zeiss haemocytometer.

### Testicular volume

Testicular volume was measured using an orchidometer (Test-Size; Resimed, Switzerland).

### Serum hormones

Serum hormone levels of FSH, LH, PRL and testosterone in the morning were measured only once.

### Statistical analysis

Statistical analysis was performed on a Macintosh computer using Student's *t*-test, Welch's *t*-test and  $\chi^2$  analysis.

## Results

There was no significant difference in the mean age between the patients with Klinefelter's syndrome and the controls

**Table 1.** Questionnaire of sexual function

1. Sexual desire
(1) normal
(2) slightly decreased
(3) major decrease
(4) none
2. Erectile function
(1) normal erection with the ability to engage in normal intercourse
(2) normal erection but shrinkage upon insertion into the vagina
(3) poor erection and inability to penetrate the vagina
(4) no erection
3. Ejaculation
(1) ejaculation occurs with normal semen volume
(2) ejaculation occurs with decreased semen volume
(3) positive orgasm but no ejaculation
(4) no ejaculation and no orgasm
4. Interval until ejaculation
(1) normal
(2) slightly premature or slightly late
(3) very premature or very late
(4) instantaneous or no ejaculation at all
5. Orgasm
(1) normal
(2) slightly decreased sensation
(3) significantly decreased sensation
(4) total lack of sensation
6. Frequency of sexual intercourse per month

( $32.2 \pm 4.0$  vs.  $33.5 \pm 4.2$  years; Student's *t*-test,  $p = 0.129$ ). The clinical features of patients with Klinefelter's syndrome are summarized in Table 2. Among these 40 patients, 38 (Cases 1–38) were pure 47,XXY, one (Case 39) was 47,XXY with a pericentric inversion of chromosome 9 and one (Case 40) was a mosaic of 46,XY/47,XXY(2:28), confirmed by FISH using sex chromosome specific DNA probes.

The semen volume of 14 cases (35.0%) was decreased while that of 26 cases (65.0%) was normal. Thirty-nine (97.5%) of the 40 cases had azoospermia. Although the karyotype of Case 38 was pure 47,XXY, he had severe oligoasthenozoospermia with a sperm concentration of  $0.9 \times 10^6$ /ml. His serum LH value was elevated, but his serum FSH, PRL and testosterone values were normal.

In the 40 patients with Klinefelter's syndrome, 39 (97.5%) had elevated blood FSH levels ( $\geq 13.7$  mIU/ml) and one case (2.5%) had a normal FSH value (1.8–13.6 mIU/ml). Thirty-six cases (90.0%) had elevated LH levels ( $\geq 8.9$  mIU/ml) and four cases (10.0%) had normal LH values (1.1–8.9 mIU/ml). Twenty-one cases (52.5%) had decreased testosterone values ( $\leq 2.69$  ng/ml) and 19 (47.5%) had normal testosterone values (2.70–10.70 ng/ml). One case (2.5%) had a decreased prolactin value ( $\leq 4.3$  ng/ml), 31 cases (77.5%) had normal

**Table 2.** Clinical features of patients with Klinefelter's syndrome

Pt. No.	Karyotype	Age	Semen analysis			Hormonal analysis				Testis	
			Volume (ml)	Sperm concentration (10 <sup>6</sup> /ml)	Sperm motility (%)	Testosterone (ng/ml)	FSH (mIU/ml)	LH (mIU/ml)	PRL (ng/ml)	Volume (ml) R	L
1	47,XXY	32	3.7	0.00		4.61	56.0	26.6	13.5	3	3
2	47,XXY	30	1.4	0.00		3.31	109.1	47.6	34.8	2	2
3	47,XXY	34	0.9	0.00		0.80	26.2	7.5	10.0	3	3
4	47,XXY	28	2.6	0.00		2.38	33.3	16.4	22.7	2	2
5	47,XXY	36	1.8	0.00		2.20	40.1	16.5	19.2	4	4
6	47,XXY	37	1.0	0.00		4.32	40.5	27.1	15.7	3	3
7	47,XXY	31	1.6	0.00		4.39	37.6	16.7	19.2	2	2
8	47,XXY	33	1.5	0.00		2.61	35.7	20.7	14.8	4	4
9	47,XXY	31	4.1	0.00		2.38	39.9	13.6	10.8	5	3
10	47,XXY	36	2.0	0.00		2.13	57.1	26.3	10.7	4	4
11	47,XXY	33	1.2	0.00		0.97	30.4	11.8	13.8	2	2
12	47,XXY	32	0.1	0.00		0.74	33.4	10.3	39.5	2	2
13	47,XXY	34	3.0	0.00		0.76	39.0	18.0	12.6	3	2
14	47,XXY	36	3.0	0.00		3.26	31.0	19.0	9.5	6	6
15	47,XXY	26	1.2	0.00		4.73	59.1	20.5	31.8	6	6
16	47,XXY	34	4.0	0.00		3.65	56.0	23.0	6.2	5	5
17	47,XXY	40	0.2	0.00		1.51	36.7	17.9	9.0	3	4
18	47,XXY	31	2.4	0.00		1.51	57.2	21.0	77.9	2	2
19	47,XXY	32	3.3	0.00		2.00	38.3	15.0	19.8	2	2
20	47,XXY	31	4.0	0.00		3.72	48.5	21.8	17.9	3	3
21	47,XXY	35	0.8	0.00		1.74	54.4	19.8	42.3	3	3
22	47,XXY	34	3.2	0.00		3.52	26.6	3.3	8.8	3	3
23	47,XXY	27	0.5	0.00		3.20	58.6	25.2	17.1	2	2
24	47,XXY	34	0.5	0.00		1.62	58.9	4.4	7.0	3	3
25	47,XXY	25	4.2	0.00		3.20	55.1	8.8	15.9	3	3
26	47,XXY	35	2.0	0.00		1.45	81.7	19.7	27.7	4	4
27	47,XXY	31	2.4	0.00		3.72	61.2	12.4	43.0	3	3
28	47,XXY	30	2.0	0.00		3.43	78.7	19.5	9.6	3	3
29	47,XXY	29	3.0	0.00		2.98	49.0	16.0	3.3	3	3
30	47,XXY	30	2.0	0.00		1.68	57.0	23.0	21.2	2	3
31	47,XXY	31	5.0	0.00		2.20	19.3	12.7	49.0	4	4
32	47,XXY	27	7.0	0.00		1.90	42.7	18.3	15.6	3	4
33	47,XXY	24	1.0	0.00		1.40	32.3	17.7	20.7	3	3
34	47,XXY	30	3.0	0.00		3.80	31.7	14.3	20.0	2	3
35	47,XXY	39	3.0	0.00		1.80	32.3	38.1	14.6	1	1
36	47,XXY	38	4.0	0.00		1.80	30.9	13.8	38.9	3	3
37	47,XXY	28	2.5	0.00		3.00	35.5	17.7	16.5	2	2
38	47,XXY	28	3.0	0.90	0.0	4.00	6.4	20.2	9.0	3	3
39	47,XXY,inv(9)(p11q13)	34	5.8	0.00		4.59	69.3	27.6	25.0	3	4
40	46,XY/47,XXY (2:28)	41	2.2	0.00		4.79	32.0	10.6	4.7	5	5

values (4.4–30.0 ng/ml), and eight cases (20.0%) had elevated values ( $\geq 30.1$  ng/ml).

All patients had very small testes with an average testicular volume of  $3.1 \pm 1.1$  ml (mean  $\pm$  S.D).

The sexual behaviour of patients with Klinefelter's syndrome is summarized in Table 3. In terms of sexual desire, 36 cases (90.0%) were normal while four cases (10.0%) had slightly decreased levels of sexual desire.

Regarding erectile function, 39 cases (97.5%) were normal with the ability to engage in normal intercourse. Only one case (2.5%) had normal erection with shrinkage upon insertion into the vagina.

With regard to ejaculation, 23 cases (57.5%) had a normal semen volume whilst 17 cases (42.5%) had a decreased semen volume. The interval until ejaculation was normal in 17 cases (42.5%), slightly premature or slightly late in 21 cases

(52.5%) and very premature or very late in two cases (5.0%). Orgasm was normal in 32 cases (80.0%), slightly decreased in seven cases (17.5%), and significantly decreased in one case (2.5%).

There was no significant difference in the frequency of sexual function disturbances between the patients with Klinefelter's syndrome and the control group (67.5% vs. 60.0%;  $\chi^2$  analysis;  $p = 0.454$ ).

**Table 3.** Sexual function of patients with Klinefelter's syndrome

Pt. No.	Sexual desire	Erectile function	Ejaculation	Interval until ejaculation	Orgasm	Frequency of sexual intercourse per month
1	1	1	2	2	2	2.0
2	1	1	2	2	1	3.0
3	1	1	2	2	2	1.5
4	1	1	1	1	1	4.0
5	1	2	2	3	1	10.0
6	1	1	1	1	2	1.5
7	1	1	2	2	1	5.0
8	1	1	2	2	2	2.0
9	1	1	1	2	1	6.0
10	2	1	2	2	1	6.0
11	1	1	2	2	1	4.0
12	1	1	2	2	3	6.0
13	1	1	1	2	1	3.5
14	1	1	1	1	1	4.0
15	1	1	1	2	1	4.0
16	1	1	2	2	1	2.0
17	1	1	2	1	1	2.0
18	1	1	1	2	1	5.0
19	1	1	1	1	2	1.0
20	1	1	1	2	1	3.0
21	2	1	2	2	2	3.0
22	1	1	1	1	1	4.0
23	2	1	1	1	1	1.0
24	1	1	1	2	1	5.0
25	1	1	1	1	1	6.0
26	1	1	1	1	1	3.0
27	1	1	1	1	1	4.0
28	1	1	2	2	1	1.5
29	1	1	1	3	1	4.0
30	1	1	2	2	1	8.0
31	1	1	1	1	1	8.0
32	1	1	1	1	1	2.0
33	1	1	2	2	1	4.0
34	1	1	2	1	1	11.0
35	1	1	2	2	2	3.0
36	1	1	1	1	1	12.5
37	1	1	1	2	1	2.0
38	1	1	1	1	1	7.0
39	1	1	1	1	1	8.0
40	2	1	1	1	1	2.0

Among the 21 Klinefelter's syndrome patients with decreased testosterone values, 16 (76.2%) had some type of sexual function disturbance. Of the remaining 19 patients with normal testosterone values, 13 (68.4%) had some type of sexual function disturbance. There was no significant difference in the incidence of sexual function disturbances between the group with decreased testosterone levels and those with normal testosterone levels ( $\chi^2$  analysis;  $p = 0.583$ ).

The mean frequency of sexual intercourse per month in the Klinefelter's syndrome patients was significantly higher than in the control group ( $4.4 \pm 2.8$  vs.  $3.3 \pm 1.6$ : Welch's *t*-test,  $p < 0.05$ ).

## Discussion

In classic Klinefelter's syndrome, the karyotype of all cells is 47,XXY. This results from either maternal or paternal meiotic non-disjunction during gametogenesis. Lorda *et al.* (1992) showed that, in patients with Klinefelter's syndrome, the extra X chromosome is derived from the mother and from the father nearly equally. On the other hand, mosaicism results from mitotic non-disjunction after fertilization. In this study, only one case was a mosaic of 46,XY/47,XXY(2:28).

Variant syndromes characterized by more than two X chromosomes are associated with more severe abnormalities than those of classic Klinefelter's syndrome (Fraccaro *et al.*, 1960). In this study, no patient had a total chromosome number  $>48$ .

Penile erection is a complex behavioural response that depends on the coordination of neural mechanisms at various levels of the neuroaxis. The central and peripheral neural pathways controlling erection are sensitive to the hormonal environment and appear to use a variety of neurotransmitters. In patients with Klinefelter's syndrome, all cells in the body, including cranial nerves, have the abnormal karyotype of 47,XXY. In this study, 27(67.5%) of the patients with Klinefelter's syndrome had some type of sexual function disturbance. However, there was no significant difference in the frequency of sexual function disturbances between the patients with Klinefelter's syndrome and the non-azoospermic infertile males who exhibited normal karyotypes of 46,XY. In most men with Klinefelter's syndrome, plasma oestradiol levels are often elevated, resulting in increased

levels of sex-hormone-binding globulin, thereby lowering free testosterone levels (Wieland *et al.*, 1980). In this study, 19 cases (47.5%) had normal testosterone levels. However, we did not investigate free testosterone in this study. We suggest that some patients with Klinefelter's syndrome have decreased free testosterone values despite normal total testosterone values. These decreased free testosterone levels may lead to the observed sexual disturbances.

On the other hand, the average frequency of sexual intercourse per month in the patients with Klinefelter's syndrome was significantly higher than was that of the non-azoospermic infertile males. A possible explanation for this variation may lie in the fact that many of these patients were diagnosed with azoospermia prior to the administration of the questionnaire and may have wished to continue to have relations as a couple.

In classic Klinefelter's syndrome, azoospermia is present in  $>95\%$  of the cases. Harari *et al.* (1995) reported that the fertilization rate with intracytoplasmic sperm injection (ICSI) using spermatozoa from a patient with mosaic Klinefelter's syndrome was high. For example, Laron *et al.* (1982) documented a case in which a patient with classic 47,XXY fathered a child, confirming the patient's paternity according to HLA typing. In the present study, one patient with classic 47,XXY had severe oligoasthenozoospermia and a normal serum FSH value. We think that after extremely careful evaluation of the sperm karyotype using the FISH technique (Chevret *et al.*, 1996), it may be possible for this patient to sire a child using ICSI (Palermo *et al.*, 1992).

After testosterone replacement therapy, patients with Klinefelter's syndrome show better overall mood, less irritability, more energy and drive, less tiredness, more endurance and strength, less need for sleep, better concentration and better relations with others, and the volume of prostate and seminal vesicles increased (Nielsen *et al.*, 1988, Sasagawa *et al.*, 1989). However, Kubler *et al.* (1992) showed that testosterone replacement does not prevent bone mineral deficiency after puberty.

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## References

- Chevret, E., Rousseaux, S., Monteil, M., Usson, Y., Cozzi, J., Pelletier, R. & Sele, B. (1996) Increased incidence of hyperhaploid 24,XY spermatozoa detected by three-colour FISH in a 46,XY/47,XXY male. *Human Genetics*, **97**, 171–175.
- Fraccaro, M., Kaljser, K. & Lindsten, J. (1960) A child with 49 chromosomes. *Lancet*, **2**, 899–902.
- Harari, O., Bourne, H., Baker, G., Gronow, M. & Johnston, I. (1995) High fertilization rate with intracytoplasmic sperm

- injection in mosaic Klinefelter's syndrome. *Fertility & Sterility*, **63**, 182–184.
- Klinefelter, H., Reifenstein, E. & Albright, F. (1942) Syndrome characterized by gynecomastia, aspermatogenesis without a-Leydigism, and increased excretion of follicle-stimulating hormone. *Journal of Clinical Endocrinology*, **2**, 615–627.
- Kubler, A., Schulz, G., Cordes, U., Beyer, J. & Krause, U. (1992) The influence of testosterone substitution on bone mineral density in patients with Klinefelter's syndrome. *Experimental & Clinical Endocrinology*, **100**, 129–132.
- Laron, Z., Dickerman, Z., Zamir, R. & Galatzer, A. (1982) Paternity in Klinefelter's syndrome—A case report. *Archives of Andrology*, **8**, 149–151.
- Lorda, S. I., Binkert, F., Maechler, M., Robinson, W. P. & Schinzel, A. A. (1992) Reduced recombination and paternal age effect in Klinefelter syndrome. *Human Genetics*, **89**, 524–530.
- Maeda, T., Ohno, M., Matsunobu, A., Yoshihara, K. & Yabe, N. (1991) A cytogenetic survey of 14,835 consecutive liveborns. *Jinrui Idengaku Zasshi. Japanese Journal of Human Genetics*, **36**, 117–129.
- Nielsen, J., Pelsen, B. & Sorensen, K. (1988) Follow-up of 30 Klinefelter males treated with testosterone. *Clinical Genetics*, **33**, 262–269.
- Palermo, G., Joris, H., Devroey, P. & Van, S. A. (1992) Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. *Lancet*, **340**, 17–18.
- Sasagawa, I., Nakada, T., Kazama, T., Terada, T. & Katayama, T. (1989) Testosterone replacement therapy and prostate/seminal vesicle volume in Klinefelter's syndrome. *Archives of Andrology*, **22**, 245–249.
- WHO: (1992) WHO *Laboratory Manual for the Examination of Human Semen and Semen-Cervical Mucus Interaction*, 3rd edn. Cambridge University Press, Cambridge.
- Wieland, R., Zorn, E. & Johnson, M. (1980) Elevated testosterone-binding globulin in Klinefelter's syndrome. *Journal of Clinical Endocrinology and Metabolism*, **51**, 1199–1200.
- Yoshida, A., Miura, K., Hara, H., Nishimi, D., Nagao, K. & Shirai, M. (1996) A cytogenetic study of azoospermic males. *Japanese Journal of Fertility and Sterility*, **41**, 164–169.
- Yoshida, A., Miura, K. & Shirai, M. (1996) Chromosome abnormalities and male infertility. *Assisted Reproduction Reviews*, **6**, 93–99.

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