Constitutional complex chromosomal rearrangements in a klinefelter patient: case report and review of literature

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Abstract

Backgrounds While XXY aneuploidy is the most common disorder of sex chromosomes in men, complex chromosomal rearrangements (CCRs) are rare in humans.

Case description Here we describe clinical and cytogenetic findings in a male referred to our cytogenetic laboratory by an infertility clinic. The patient's age was 35 at the time of referral. Total azoospermia was confirmed on semen analysis.

Results The karyotype of peripheral blood showed 47,XXY, t(1;3;5)(p22;q29;q22). The mother had the same CCRs.

Discussion To our best of our knowledge this is the first case of 47,XXY with CCRs. We think it is important to report such a unique chromosomal occurrence.

Keyword Complex chromosomal rearrangements · Klinefelter · Azoospermia

Introduction

While single chromosome translocations are observed rather frequently in human, complex chromosomal rearrangements (CCRs) which is defined as translocation between at least three chromosomes are found rarely. The frequency of CCRs in general population is unknown. However, from the large survey of 269371 prenatal diagnosis 7 fetuses had *de novo* CCRs which is about 0.003% [1].

Balanced carriers of CCRs usually may have normal phenotype but often subfertility/infertility due to meiotic arrest and recurrent miscarriages in females are the main reasons for the detection of balanced CCRs [2].

CCRs usually occur *de novo* [3]. This may be due to severe reproductive impairment through meiotic disturbance or chromosomal imbalance in gametes. Familial transmission has been documented mainly in female [4]. Nevertheless transmission through males has been reported in a few published cases [5]. Therefore, this is assumed that CCRs may be formed mainly during spermatogenesis but transmitted in families through oogenesis [6]. But very interestingly, the chromosomes involved in CCRs are often preferentially of paternal origin [4].

CCRs can be classified based on the number of chromosome breaks: those with four or fewer breaks (mainly seen in balanced female carriers), and those with more than four breaks (mostly detected in *de novo* CCRs) [7].

CCRs have also been categorized into three classes by Kausch et al. (1988) [8]. The first class is three-way rearrangements which include three chromosomes break and exchange chromosomal segments. This class of CCRs is mainly familial [9].

The second class is exceptional CCRs in which more than one breakpoint per chromosome is found and as many as 7 chromosomes with as many as 15 breakpoints can be involved [6] and mainly detected in *de novo* CCRs [10].

Capsule The concurrence of complex chromosomal rearrangements (CCRs) with sex chromosome aneuploidy has not been reported before. This is the first report of CCRs with an extra chromosome X in an infertile male.

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The third class is double two-way translocations [6] in which two or three independent, simple reciprocal or Robertsonian translocations present in a carrier (eg [11]).

Although CCRs are rare, aneuploidy 47,XXY is the most common abnormality of sex chromosomes in humans. Most XXY cases have developmental delay, hypogonadism and gynecomastia, infertility, behavioral or psychiatric disorders, elevated average height (179.2 ± 6.2 cm) and increased plasma gonadotrophins [12].

We report a klinefelter case with an apparently balanced CCR, with three breakpoints involving three chromosomes 1, 3, and 5.

Case report

The case presented here is a 35 year old man referred to our cytogenetic laboratory by an infertility clinic. He was married to a woman who had a healthy child from previous marriage. He was born from a full term natural delivery with no apparent complication. The age of his mother at this pregnancy was 33.

The parents were unrelated. The mother had one spontaneous abortion. The case was the only child. Developmental milestones were retarded (eg. walking at 30 months). Language was delayed. He had learning difficulties at school especially at mathematics and could finish only primary school.

The semen analysis showed azoospermia. Serum testosterone and prolactine were within normal range (7.3 ng/ml, and 4 ng/ml respectively with normal male range 3–20 and 1–18 respectively using ELISA method). Serum FSH and LH were elevated using ELISA method (29.3 mIU/ml and 13.4 mIU/ml respectively with normal male range 1–14, and 0.6–8.1 respectively). His height was 185 cm. According to his wife his social judgment was partially impaired.

Cytogenetic analysis

Chromosomal analysis was performed on phytohemagglutinin (PHA)-stimulated peripheral lymphocyte cultures using standard cytogenetic methods [13, 14].

Fig. 1 The karyotype [47,XXY,t(1;3;5)(p22;q29;q22)] of the proband

Briefly, peripheral blood lymphocytes were cultured in 5 ml RPMI 1640 (GIBCO), supplemented with 20% (v/v) fetal bovine serum (GIBCO) and 10 µg/ml phytohaemagglutinin (GIBCO) at 37°C. After 72 h of incubation 40 µl colcemid (10 µg/ml, GIBCO) was added to the cells. The cells were incubated at 37°C for about 10 mins. The suspension was centrifuged, and the pellet was resuspended in 5–10 ml KCL (0.075 M) for about 20 mins at 37°C. After centrifugation the cells resuspended in fixative (3v methanol: 1v acetic acid, Merk). The fixative was changed at least 3 times. Using a Pasteur pipette, a drop was dropped onto the slide. The chromosomes were viewed under phase contrast to assess quality of the metaphases and nuclei. The chromosomes were treated with trypsin then stained by Giemsa (GTG banded) after aging. Thirty metaphases were analyzed at resolution 550 bands.

Metaphases from the case revealed that an extra band [5 (q22qter)] had been added to 1p22, the segment between 1p22 to 1pter had been added to 3q29 resulting to the formation of two chromosomes 1 and 3 with addition and chromosome 5 with deletion. Therefore, the karyotype of the case was ascertained as: 47, XXY,t(1;3;5)(p22;q29;q22) (Fig. 1) according to The International System for Human Cytogenetic Nomenclature ISCN 2005[15].

The karyotype of the mother was: 46, XX,t(1;3;5)(p22;q29;q22) (Fig. 2). The father had normal male karyotype.

The chromosomes involved in these CCRs are shown in Fig. 3.

Discussion

Most of the CCRs found to be transmitted maternally since CCR male carriers are at increased risk of primary infertility or subfertility [16].

The pregnancy outcome for carriers of balanced CCRs remains highly empirical and so the genetic counseling is very difficult for CCRs cases. In a study done by Gorski et al. (1988) 25 families with CCRs had in total 67 pregnancies. The spontaneous abortions were 48.3% and 18.4% of the live born babies had malformation 16 [6].

Batista et al. (1994) reported that of the 63 live born children of CCRs carriers 27% had normal karyotypes, 31.7% had the same balanced CCRs and 41.3% had unbalanced karyotypes [4].

There is a high prevalence of maternal origin in familial CCRs (as in our case) and a high incidence of mental

Fig. 2 The karyotype [(46,XX,t(1;3;5)(p22;q29;q22)] of the mother

retardation and phenotypic abnormalities in *de novo* CCRs. However, CCRs can also be found in phenotypically normal individuals [2].

Occurrence of klinefelter with simple translocations has been reported in few published cases. For example, 4, XXY plus a translocation between 15q22 and 17q21 was reported by Garcia et al. (1996) [17].

48,XXXY,t(1;7)(q42;q32)pat[71%]/47,XXY,t(1;7)(q42;q32)pat[29%] was detected in a case clinically suspected to be klinefelter [18]. Two cases of klinefelter syndrome plus a robertsonian translocation between chromosome 13q;14q and 13q;15q [46,XXY,t(13q;14q) and 46,XXY,t(13q;15q)] were reported [19, 20].

A translocation between chromosomes 18 and 21 plus 47,XXY was also reported [21].

A 48,XXXY case carrier for a translocation between chromosome X and 9 is the only one representing X-autosome translocation in a klinefelter proband [22].

To our best knowledge, our case is the only one to be the combination of 47,XXY and complex translocations.

The number(s) of translocation carrier cases with breakpoints at 1p22 is 2, at 3q29 is 3, and at 5q22 is only 1 [23].

Therefore, our case is probably the second case of the translocation at 5q22 reported so far.

Both XXY karyotype and CCRs often lead to severe reproductive impairment because of meiotic disturbance or production of unbalanced gametes. There are only a few reported cases of male carriers of CCRs with no infertility [23, 24]

Therefore, it is not clear whether the azoospermia of our patient is due to having an extra X or CCRs or the combination of both. It is obvious that the risk of producing abnormal offspring is quit high because of this CCR even if sperm could be recovered by testicular biobsy.

Most of the CCRs occur *de novo* during spermatogenesis and are transmitted in families through oogenesis. However, it is worth to mention that some of the preimplantation genetic diagnosis (PGD) results indicated that as high as 90% of chromosomal abnormalities (some of them complex rearrangements) due to high mitotic chromosome instability [25] which may have potential to subsequently lead to the formation of *de novo* CCRs in embryos.

Giardino et al., (2009) have pointed out that chromosomes 2, 3, 4, 7, 11 are more frequently implicated in CCRs

Fig. 3 Partial karyotype of the CCRs and ideograms of chromosomes 1, 3, and 5. The arrows point to the breakpoint at each chromosome

than others [1]. Interestingly one of the chromosomes involved in our case is chromosome 3.

The mechanism of coincidence of this maternal CCR and an extra chromosome X in the patient reported here is unclear since we do not know the paternal or maternal origin of this extra X chromosome. However, it is more likely that the origin is maternal since the maternal CCRs could have led to meiotic nondisjunction due to interchromosomal effect.

As it mentioned before spermatogenesis dysfunction in translocation male carriers is one of the main obstacles in male fertility. This problem can be overcome by employing intracytoplasmic sperm injection (ICSI). However, theoretically a successful result of ICSI for CCRs male carriers is very unlikely, and so far only one case of ICSI in a male carrier of a CCRs which led to the birth of a normal progeny with the same balanced CCR as her father has been reported [26]. In addition, PGD of embryos has been applied in couples with CCRs [27]. However, ICSI and PGD are not feasible for CCRs cases in our country. Therefore, the couple decided to select a donated embryo with no genetic imbalance and hence increase their chances of a successful pregnancy.

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