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Case report

A man with 47,XYY karyotype, prolactinoma and a history of first trimester recurrent miscarriages in his wife

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ABSTRACT

The clinical and laboratory features as well as the diagnostic and therapeutic approach of men with XYY syndrome have not been fully described. A 41-year-old infertile man was diagnosed as having a 47,XYY karyotype and a micro-prolactinoma. His 32-year-old wife had a history of five spontaneous pregnancies, all resulting in first trimester miscarriages. Three in-vitro fertilization (IVF) attempts were made with no biochemical pregnancy. During the third attempt, a pre-implantation genetic diagnosis (PGD) was performed by fluorescent in-situ hybridization (FISH) technique. Only one out of six (16%) embryos had normal karyotype. CONCLUSIONS: (1) Karyotypic analysis of both partners is a *sine qua non* investigation for recurrent miscarriages; (2) the XYY syndrome results in high frequency of embryo aneuploidy; (3) PGD by FISH can contribute to the transferring of chromosomally normal embryos in cases of parental chromosomal defects; (4) investigation for a prolactinoma should be considered in men with XYY syndrome.

Key Words: Fluorescent in-situ hybridization (FISH), Karyotype, Pre-implantation genetic diagnosis, Prolactinoma, Recurrent miscarriage, XYY syndrome

INTRODUCTION

XYY syndrome is a chromosomal aberration of the sex chromosomes in which men receive an extra Y chromosome. The 47,XYY karyotype is found in 1 out of 1,000 male live births.[1] XYY men appear to be physically normal, usually tall and thin, with normal gonadal function. Central nervous system function is generally normal, although cases of hyperactivity, hypotonia, tremor, mild learning disability, delayed speech/language skills, autism and myotonic dystrophy have been reported.[2,3] The majority of XYY men are fertile. Nevertheless, there have been reported cases of infertile men with severe oligo-asthenoteratozoospermia or even azoospermia.[4] They have chromosomally normal children as less than 1% of 24,YY and 24,XY karyotypes are detected in sperm by fluorescent in-situ hybridization (FISH),[5] while a chromosome 13 aneuploidy in sperm was detected in one case.

Prolactinomas constitute 40-60% of pituitary

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tumors. They are composed mainly of lactotroph cells and secrete prolactin. The phenotype in males consists of secondary hypogonadism and, in cases of macro-prolactinomas (tumors more than 10 mm in diameter), of pressure symptoms such as headaches and visual field defects.[6]

In this report, we present the case of a 41-year-old man with a 47,XYY karyotype and prolactinoma, whose spouse had a history of first trimester recurrent miscarriages.

CASE REPORT

A couple was referred to our Unit in 2009 due to secondary infertility. The personal medical history of the 41-year-old man was unremarkable and his sexual development was normal. He was tall (height 1.90 m) and obese [weight 140 kg, body mass index (BMI) 38.8 kg/m^2], with normal testicular volume (25 ml each). Basal hormone profile included: serum follicle stimulating hormone (FSH) 3.5 U/l, luteinizing hormone (LH) 2.3 U/l, total testosterone (T) 4.5 nmol/l, prolactin 2.8 nmol/l (reference range <1.0), thyroid stimulating hormone (TSH) 1.8 U/l, free thyroxine (FT_4) 19.3 pmol/l and free triiodothyronine (FT_3) 4.9 pmol/l. Several semen samples were collected by masturbation after three to four days of abstinence. Semen volume ranged from 0.8 to 3.2 ml, sperm concentration from 10.0 to 93.1x10^6/ml, motility from 2 to 70% and normal morphology from 30 to 50%. His karyotype was 47,XYY. Due to hyperprolactinemia, a pituitary magnetic resonance imaging (MRI) was performed and a micro-adenoma of 6 mm diameter was found. As the diagnosis of micro-prolactinoma was set, the man was started on quinagolide 75 mg once daily. Serum prolactin levels were normalized at 0.6 nmol/l as well as T levels at 15.5 nmol/l. A second MRI, twelve months later, showed that the micro-adenoma was reduced to 4 mm.

His 32-year-old wife was also obese (height 1.62 m, weight 120 kg, BMI 45.7 kg/m^2) with normal menstrual history. She had five spontaneous pregnancies between the years 2002-2008, with the same spouse, all resulting in first trimester miscarriages. The cause of the first trimester miscarriages remained unknown despite an investigation that included hematological, biochemical, hormonal and immunological profile as well as imaging procedures. Basal hormone profile included: FSH 5.9 U/l, LH 3.3 U/l, T 1.6 nmol/l, prolactin 1.1 nmol/l, progesterone 18.8 nmol/l (day 21 of the menstrual cycle), TSH 1.6 U/l, FT_4 19.3 pmol/l and FT_3 4.5 pmol/l. Her karyotype was 46,XX. During the same period (2002-2008) she underwent two in-vitro fertilization (IVF) attempts, both resulting in embryo transfer but neither one in biochemical pregnancy. After the second IVF attempt, the wife had her fourth spontaneous pregnancy at which time a 47,XYY karyotype was detected in her husband. This pregnancy also resulted in an abortion and the karyotype of the miscarried embryo was 46,XY [19 cells]/47,XY+21 [2 cells]. A third IVF attempt was made and a pre-implantation genetic diagnosis (PGD) was performed by FISH technique. Standard informed consent was signed prior to the procedure. Only one out of six embryos was normal (16%) (Table 1) and was transferred but, unfortunately, no clinical pregnancy ensued.

Table 1. Pre-implantation genetic diagnosis (PGD) by fluorescent in-situ hybridization (FISH) during the third in-vitro fertilization (IVF) attempt

Embryos	Chromosomes							Comments
	sex	13	15	16	17	18	21	22	
1.	XXX	3	3	3	3	3	3	3	triploid
2.	XYY	2	2	2	2	2	2	2	XYY syndrome
3.	XYY	2	2	2	2	2	2	2	XYY syndrome
4.	XYY	2	2	2	2	2	2	2	XYY syndrome
5.	XY	2	2	2	2	2	2	2	normal male
6.	XX	1	2	2	2	2	2	3	multiple anomalies

DISCUSSION

We present a 41-year-old man with a 47,XYY karyotype and prolactinoma, whose spouse had first trimester recurrent miscarriages.

Although mild central nervous system abnormalities have been reported, men with XYY syndrome have, in the vast majority of cases, a normal phenotype. Nevertheless, in a recent study, intellectual functioning of children with XYY syndrome, as measured by the revised Wechsler Intelligence Scale (full scale intelligence quotient), was approximately 60 as compared to 100 of the controls.[7] This lack of specific phenotype results in approximately 85% of XYY men remaining undiagnosed.[8] In our case, the diagnosis was not established until investigation for first trimester recurrent miscarriages was carried out.

As far as reproduction is concerned, XYY men are considered fertile, although not invariably.[1] The 47,XYY karyotype has an estimated frequency of 0.2-0.5% among subfertile men.[4] Although the man in our case had variations in the semen parameters (i.e. different degrees of oligo-astheno-teratozoospermia at various time periods), pregnancy was achieved either spontaneously or by IVF.

Despite the XYY karyotype, spermatogenesis in affected men results mainly in 23,X and 23,Y sperm as the supernumerary Y is eliminated during meiosis.[9] However, in a recent study, a 38% frequency of sex and autosomal chromosome aneuploidy was detected in the sperm of XYY men as compared to 1% in the controls.[10] In the same study, the frequency of embryos with aneuploidy was 32%. Unfortunately, we did not have the opportunity to study sperm for aneuploidy in the present case. However, the frequency of aneuploidy in the embryos was high (5 out of 6 embryos, 83%), this being the probable cause of the recurrent first trimester miscarriages.

The micro-prolactinoma in our case did not affect fertility as the couple was able to achieve spontaneous pregnancies both before and after treatment with quinagolide. Initially, we thought that the prolactinoma was an incidental finding, not connected in any way to the XYY syndrome. Nevertheless, a literature search revealed two other cases of XYY syndrome and prolactinoma co-existence.[7] Prolactinoma cell lines may have aneuploidy of autosomal chromosomes, mainly chromosomes 5, 8 and 12, at a percentage of up to 78%.[11] Of course, this tumor cell aneuploidy is a common finding and does not reflect karyotypic abnormalities in peripheral blood lymphocytes, as in our case. This sparse evidence is not adequate to provide the basis for an etiological relation between prolactinoma and XYY syndrome.

Many pitfalls in the diagnostic and therapeutic approach of this case can be pointed out. For example, a karyotype analysis was offered to the woman after her second miscarriage, but not to her spouse. As a consequence, the recurrent miscarriages were classified as "idiopathic" and not of genetic origin. The husband's karyotype had not been checked and was found to be abnormal only after the fourth miscarriage. It was only then that the karyotype of the miscarried embryo was also analyzed. As far as the therapeutic approach is concerned, it is difficult to understand the rationale of performing IVF in a case of first trimester abortions. Most probably, the attending physicians considered this technique as an option to confront "idiopathic infertility", although this was clearly not the case.

According to the royal college of obstetricians and gynaecologists,[12] the investigation for recurrent miscarriages should include peripheral blood karyotyping for both spouses, cytogenetic analysis of the products of conception, pelvic ultrasound to assess uterine anatomy and morphology and investigation for primary antiphospholipid syndrome. The latter is confirmed by having two positive tests at least six weeks apart for either lupus anticoagulant or anticardiolipin antibodies of IgG and/or IgM class, in medium or high titer.

The obvious choice for the next reproductive attempt in the couple in our case would be IVF followed by PGD. The reason for selecting IVF is to have the opportunity to apply PGD as this constitutes the only way to ensure that chromosomally normal embryos will be transferred. Intra-uterine insemination using donor sperm is an attractive alternative since it would be characterized by ease of application, no need for PGD, high probability of success and low cost as compared to the IVF/PGD approach.

In conclusion, the clinical implications of this case can be summarized as follows:

- Karyotype analysis of both partners is a *sine qua non* in the investigation of recurrent first trimester miscarriages;
- XYY syndrome results in high frequency of embryo aneuploidy;
- PGD by FISH can greatly contribute in selecting and transferring chromosomally normal embryos in cases of parental genetic defects;
- Investigation for pituitary tumors, in particular prolactinomas, should be considered in men with XYY syndrome.

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