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CASE REPORT

Different clinical presentation of Klinefelter's syndrome in monozygotic twins

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Summary

There is a wide variability in the clinical presentation of Klinefelter's syndrome. We report the case of a 45-year-old man who was incidentally diagnosed a 47, XXY/46,XY karyotype in a bone marrow aspiration (case 1). He presented hypogonadic features with undetectable testosterone levels and a height in accordance with mid-parental height. He had a monozygous sibling (case 2) who did not show clinical signs of hypogonadism and whose height exceeded mid-parental height. Both patients had presented language disorders since childhood. The karyotype of lymphocytes in peripheral blood of both subjects was compatible with mosaic Klinefelter's syndrome (46,XY/47,XXY). Testosterone replacement was initiated in case 1. Lack of testicular involvement due to mosaicism and the overexpression of the SHOX gene in case 2 could explain the marked differences in phenotype in these homozygous twins.

Introduction

Klinefelter's syndrome is the most common form of male hypogonadism and of chromosome aneuploidy (0.15%) in human beings (Philip *et al.*, 1976; Perwein, 1984; Bojesen *et al.*, 2003). Nevertheless, many cases remain undiagnosed because of substantial variation in clinical presentation and lack of professional awareness of the syndrome itself. For this reason, only 10% of cases are diagnosed during puberty, usually those with greatest phenotypic expression, characterised by slow, incomplete pubic development, gynaecomastia and small, hard testes. A large proportion of cases are identified in adulthood, and many remain undiagnosed. Those detected in adulthood are generally mild forms that tend to be detected as a result of infertility (Abramsky & Chapple, 1997; Bojesen *et al.*, 2003). We present the cases of twin brothers with a karyotype consistent with mosaic Klinefelter's syndrome incidentally diagnosed in adulthood, but with very different degrees of phenotypic manifestation.

Subjects and methods

Case 1

The patient was a 45-year-old man undergoing medical assessment for a mild anaemia. He had a total haemoglobin level of 11.2 g dl^{-1} and a mean corpuscular volume of 85 fl. Complementary examinations (serum ferritin, vitamin B12 and folate levels, reticulocyte count, Coombs test, peripheral smear, liver enzymes, gastric and colonic endoscopy) did not reveal any relevant findings. A bone marrow aspiration was then performed, and it suggested iron deficiency and it also described a 47,XXY karyotype in all 50 metaphases evaluated. He reported no harmful addictions and had a history of hepatitis B. He had 4 siblings, including an identical twin, none of whom had any relevant medical history. The patient referred to incomplete pubertal development (no increase in testis size, no hair growth in androgynous zones). He reported a decreased sex drive throughout his life, a primary failure of ejaculation and denied any sexual activity. He had

elementary school education and had required speech therapy and remedial education during his childhood. On physical examination, the following data were collected: height, 175 cm; weight, 65.3 Kg; arm span, 170 cm; testicular volume of 3 ml with increased consistency; gynoid body fat distribution; bilateral gynaecomastia without nodularity; and lack of facial and body hair. The patient had noticeably slow, halting speech and difficulty rolling the letter 'R'. Cytogenetic study of lymphocytes in peripheral blood was consistent with mosaic Klinefelter's syndrome (46,XY/47,XXY) with 88% of the metaphases evaluated showing a 47,XXY karyotype. His free plasma testosterone levels were undetectable and gonadotropins were increased (LH: 21.6 U l^{-1} and FSH: 39 U l^{-1}). Bone density testing revealed severe osteopenia in the femoral neck (T score: -2.48, Z score: -2.05) and moderate in the lumbar spine (T score: -1.5, Z score: -0.72). After hormone replacement therapy with intramuscular testosterone enanthate monthly, the patient reported improved quality of life, increased muscle mass and facial and body hair growth.

Case 2

The index patient's twin brother was asked to attend our clinic for medical evaluation. The subject had no relevant medical history. Based on a medical report indicating the existence of only one placenta at birth, the twins were assumed to be monozygous. During childhood, his growth paralleled that of his twin (Fig. 1). He had a speech disorder similar to his brother's and had also required speech therapy. After the age of 12 years, his secondary sexual characteristics began to develop and he experienced a growth spurt. At age 18, the patient had the sexual phenotype of an adult and was taller than his brother (Fig. 2). The patient did not refer to any sexual dysfunction or decreased libido. However, he had never attempted to have children. On physical examination, the patient was 195 cm tall, 20 cm more than his twin brother (Fig. 3), weight 85 kg and an adult sexual phenotype with testicular volume of 17 ml. Laboratory findings confirmed normal testosterone levels (8.3 pg ml^{-1} free testosterone). A sperm test showed an ejaculated volume of 3.8 ml ($N > 1.5$), total sperm count of 1268.3×10^6 ($N > 39$) and a concentration of 333.8×10^6 ($N > 15$). Morphologic parameters were in the lower limits of normality (4% of normal), and mobility and vitality were optimal (WHO, 2010). The karyotype of lymphocytes in peripheral blood was consistent with mosaic Klinefelter's syndrome (46,XY/47,XXY) with 64% of metaphases showing a 47,XXY karyotype.

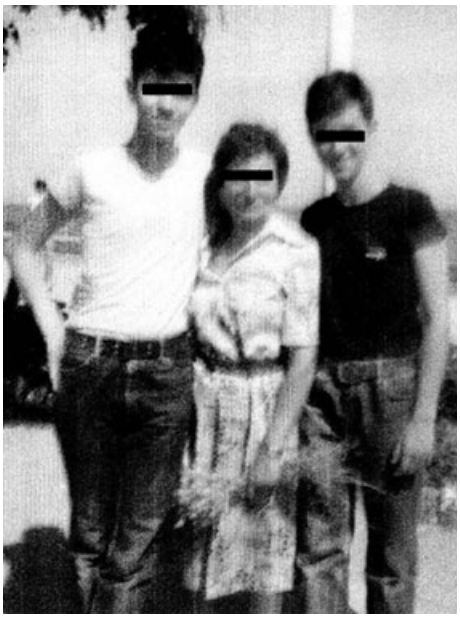

Fig. 2 Patients at the age of 18.

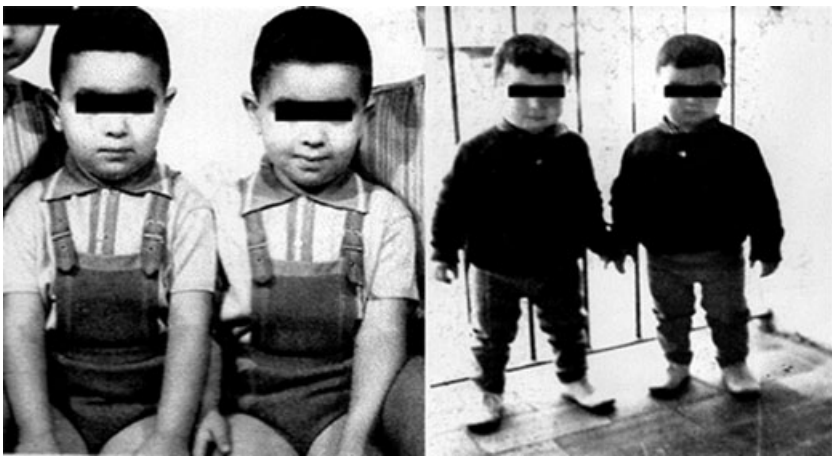

Fig. 1 Patients during childhood.

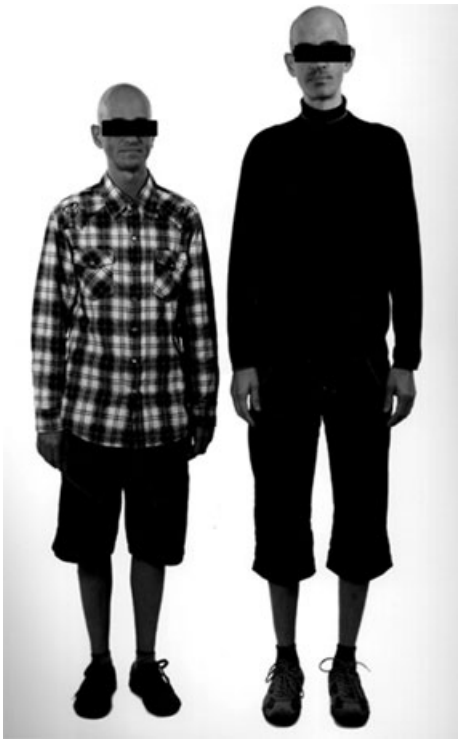

Fig. 3 Patients at the age of 45.

Discussion

The 46,XY/47,XXY mosaicism detected in the two reported cases is present in 10% of patients with Klinefelter's syndrome and is the second cause of the chromosomal anomaly detected in these patients (Abramsky & Chapple, 1997; Bojesen *et al.*, 2003). The mosaicism originates after fertilisation and is caused by a mitotic nondisjunction in the developing zygote. The 47,XXY karyotype is characteristic of the classic form of Klinefelter's syndrome and occurs in 80% of cases (Foresta *et al.*, 1998; Nieschlag *et al.*, 2000; Kamischke *et al.*, 2003). It originates from meiotic nondisjunction of the sex chromosomes during gametogenesis, either during spermatogenesis or during oogenesis (Fig. 4a) (Griffin & Wilson, 2002). The most logical explanation for the presentation of the same mosaic in identical twins is that after the formation of a chromosomally normal zygote (46,XY), a nondisjunction occurred during a mitotic division that resulted in one embryo with a normal cell line (46,XY) and the other with aneuploid (47,XXY) cell line. A later bipartition of these cells would then form 2 embryos with this mosaic (Fig. 4b). Other possible mechanisms include the formation of a 47,XXY zygote after nondisjunction or meiotic disjunction of the oocyte or spermatozoid, and this zygote should loose an X chromosome during mitotic

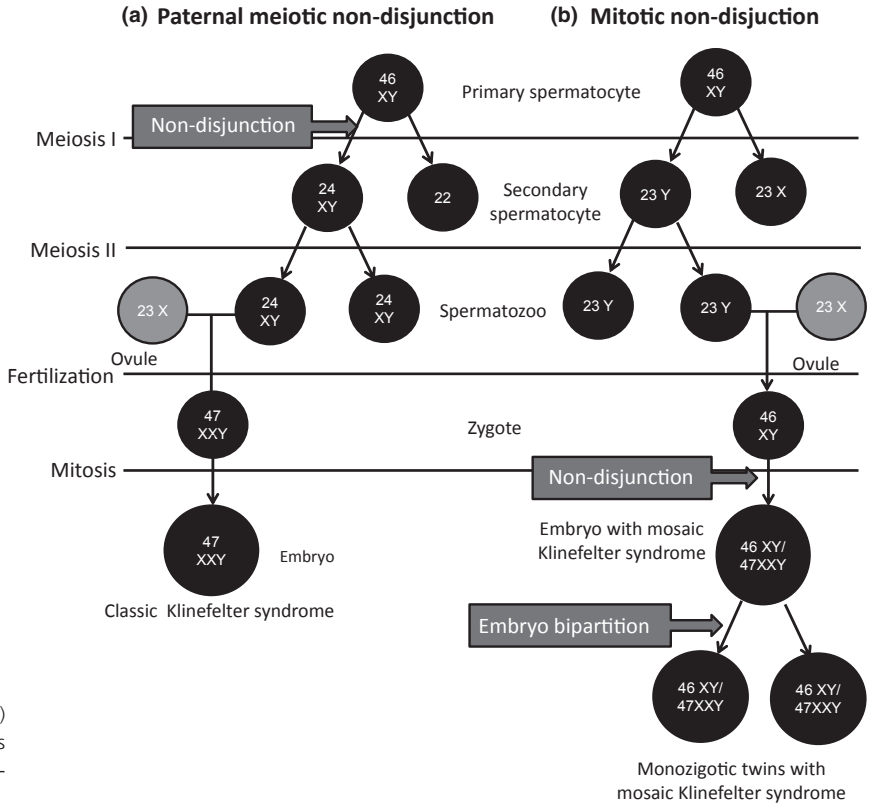

Fig. 4 Effects of meiotic and mitotic nondisjunction leading to classic (a) and mosaic (b) Klinefelter's syndrome. Circles represent cells of gametes, zygotes or embryos, with chromosomal complement indicated.

divisions resulting in a embryo with a 46,XY/47,XXY mosaicism that would then split and form two embryos carrying the mosaicism. Another possible explanation would be a mitotic nondisjunction occurring in both embryos after bipartition.

Several factors could explain the phenotypic variations in Klinefelter's syndrome. One of the key factors is the X-linked androgen receptor, which is linked to a polymorphic chain of cytosine-adenine-guanine (CAG) nucleotide repetitions. The length of this polymorphic chain is inversely related to the activity of this receptor (Hickey *et al.*, 2002). This could explain the wide clinical variations in the classical forms of Klinefelter's syndrome, that is, those in which all cell lines are affected: some cases are diagnosed during puberty owing to very obvious hypogonadism, others are not diagnosed until adulthood in the context of infertility, and a large proportion are most probably never diagnosed (Perwein, 1984; Bojesen *et al.*, 2003). Nevertheless, this could not explain the differences found in the two cases presented here because identical twins would necessarily possess the same number of repetitions of the polymorphism. Probably the key factor in these two cases was the degree to which the testicular tissue was affected by the mosaicism. When the majority of the testicular cells are affected by 47,XXY euploidy, the patient presents a more recognisable phenotype, as in the index case. On the other hand, when there is scant or null effect of the mosaic on the testes, as described previously, patients will present an apparently normal phenotype and fertility, as occurred in case 2 (Kaplan *et al.*, 1963; Kamischke *et al.*, 2003). In this respect, mosaicisms have been described in patients with Turner's syndrome (46,XX/45,X) or Down's syndrome (Silva *et al.*, 2011) as a cause of phenotypic discordance in monozygous twins. We report herein the first case of 47,XXY/46,XY mosaicism.

Clinical manifestations of Klinefelter's syndrome are determined by genes that are not inactivated in the extra X chromosome. One of these is the SHOX (short stature homebox-containing) gene, which is responsible for the short stature characteristic of Turner's syndrome (45,X0) (Ellison *et al.*, 1997). Overexpression of this gene explains the normal stature of patients with Klinefelter's syndrome, rather than the typical eunuchoid proportions of short stature and an arm span that exceeds height (Lanfranco *et al.*, 2004). Patients with Klinefelter's syndrome who receive testosterone treatment during puberty have a higher growth spurt. Therefore, the lack of hypogonadism in case 2 may explain why he was taller than his twin brother and of mid-parental height (Aksglaede *et al.*, 2011).

Patients with Klinefelter's syndrome present neurocognitive alterations: not a general reduction in intellectual abilities, but deficiencies in very specific cognition domains, mainly speech and executive functions. Many patients require speech therapy and special education in childhood (Bender *et al.*, 1986; Rovet *et al.*, 1996) as in the two cases presented here. Contradictory data have been reported on the benefits of testosterone replacement on speech disorders (Nielsen & Pelsen, 1987; Ross *et al.*, 2008). The fact that both twins had verbal dysfunction, although only one was hypogonadal, suggests that testosterone may not be a determining factor.

In conclusion, these cases are exceptional because two unusual circumstances must have occurred in the embryonic period: first, a mitotic nondisjunction and then a bipartition of the embryo. Moreover, lack of testicular involvement due to mosaicism and the overexpression of the SHOX gene in case 2 could explain the marked differences in phenotype in these homozygous twins.

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