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Antenatally Detected Klinefelter's Syndrome in Twins

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Abstract. An increased incidence of twinning has been reported among patients with Klinefelter's syndrome (XXY) and their relatives, but no data have been reported about the incidence of XXY among twins. Results from our institution's antenatal testing clinic provide data about twins and XXY. In 1842 pregnancies tested, 21 were noted to be twin gestations. Five fetuses with XXY were detected in all pregnancies, of which there was a pair of MZ twins concordant for XXY and a pair of DZ twins discordant for XXY. The incidence of XXY in twins was thus 7.1%. The fetal phenotype of XXY was examined in aborted MZ twins and found to be mild. Notably, the testicular histology was normal. These cases confirm the previously reported association of twinning and XXY. The association of twinning and XXY implies a commonality of causation; however, a maternal age effect cannot be excluded. Our data suggest that there is an increased risk of XXY among twins.

Key words: Klinefelter's syndrome, Twins, Antenatal testing, Chromosome abnormalities, Testicular development

INTRODUCTION

An increased incidence of twinning has been reported among patients with Klinefelter's syndrome (XXY) and in their families [1,3,6,8]. To our knowledge, no data exist about the incidence of XXY among twins. We report our experience with antenatal detection of XXY in twin pregnancies. This experience demonstrates an increased incidence of XXY among twins. Additionally, it affords an opportunity for analysis of the fetal phenotype of XXY.

MATERIALS AND METHODS

Cases were ascertained from the Antenatal Testing Clinic of the Medical College of Virginia. Advanced maternal age (greater than 34 years) was the most frequent indication for

antenatal testing; previous chromosomally abnormal offspring or a family history of same was the other usual indication for testing. Gestational age and presence of multiple fetuses were determined by ultrasound examination. Amniocenteses were performed in standard fashion. Karyotypes were examined in cultured amniocytes.

CASE HISTORIES

A total of 1842 pregnancies were tested. Twenty-one of these were twin gestations. In the 1821 singletons, two cases of XXY were detected. Three cases of XXY were found in the 42 twins tested, an incidence of 7.1%. A pair of MZ twins were concordant for XXY and a pair of DZ twins were discordant for XXY. These cases are reported in detail below.

Case 1 (L-A & L-B)

Oriental twins concordant for XXY were detected on amniocentesis performed at 16 weeks gestation because of advanced maternal age. The mother was a 35-year-old G5P2A3 woman taking methimazole for treatment of Grave's disease. There was a family history of twinning (Fig. 1) but not of any chromosome anomalies. After counseling, the parents elected to terminate the pregnancy at 20 weeks gestation. The placentas were separate, that is, diamniotic, dichorionic. There was velamentous insertion of the umbilical cord of twin A, and marginal insertion of the cord in twin B. Both cords had two arteries and one vein. Measurements were appropriate for gestational age: twin A weighed 416 g, twin B weighed 403 g. Body length of both fetuses was 27.0 cm. Arm span of twin A was 26.3 cm; that of twin B was 26.0 cm. Phallic lengths were both 0.9 cm. Physical features relevant to the phenotype of XXY are summarized in Table 1. Fetus B was also noted to have a small pectus excavatum while A did not. Fingertip dermatoglyphics were obscure due to gestational age.

TABLE 1- Phenotype of Klinefelter's Syndrome [7]

| | Cases | | |
|-----------------------------------|-------|-------|--------|
| | L - A | L - B | BB - J |
| Length > 95% | - | - | - |
| Arm span ≤ height | + | + | - |
| Lower body segment > upper | - | - | - |
| Brachycephaly | - | + | - |
| Low nuchal hairline | NA | NA | + |
| Minor auricular anomaly | + | + | + |
| 5th finger clinodactyly | + | + | - |
| Radioulnar synostosis | - | - | - |
| Small phallus | - | - | - |
| Hypospadias | - | - | - |
| Undescended testes | + | + | - |
| Decreased number of spermatogonia | - | - | NA |
| Dermatoglyphics: | | | |
| Simian crease | - | + | - |
| Low fingertip ridge count | NA | NA | NA |
| Hypothenar pattern | - | - | NA |
| Distal palmar triradius | - | - | NA |

NA = Not applicable, not available.

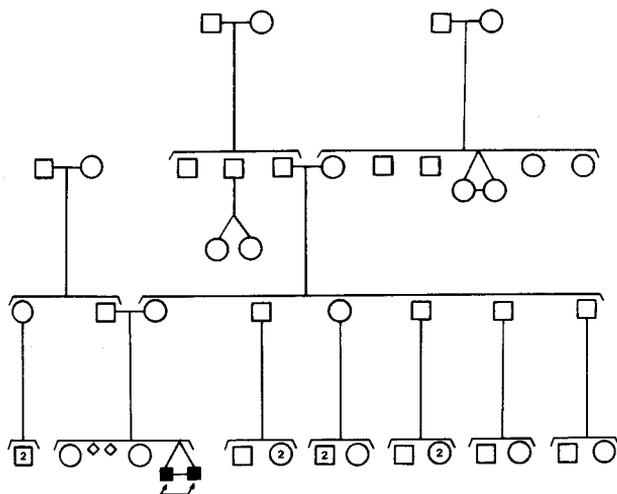


Fig. 1 - Case 1: family history of twinning.

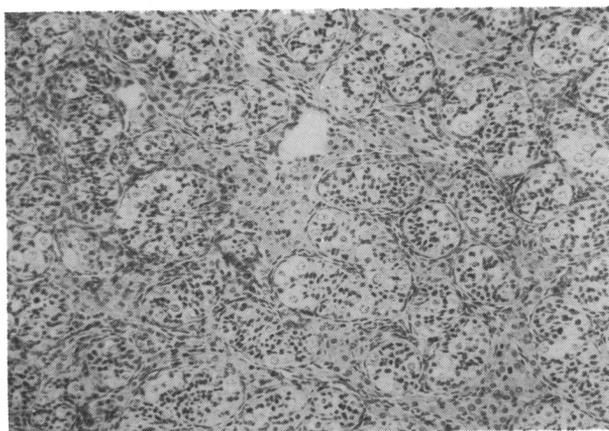


Fig. 2 - Case 1: testicular histology.

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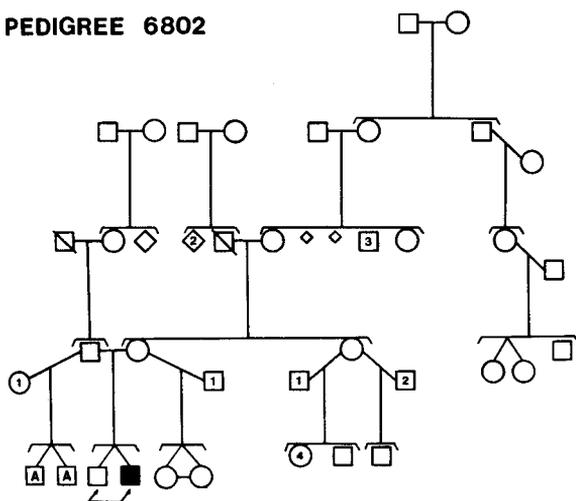


Fig. 3 - Case 2: family history of twinning.

No internal malformations were noted on gross dissection. Absence of radioulnar synostosis was documented on careful dissection. Particular attention was devoted toward examination of the genito-urinary tract, which was structurally normal. The testes were undescended, which is not unusual in fetuses of 20 weeks gestation. The testicular histology (Fig. 2) was normal for 20 weeks gestation. Neuropathological studies were also normal. Genotyping was consistent with monozygosity (Table 2). Karyotype from culture of fetal fibroblasts confirmed that both fetuses were 47,XXY.

TABLE 2 - Family 6665 - Genotyping

| | ABO | Rh | MNSs | Kell | Duffy | Jka | P | | | |
|-------------|----------------|---------|------|------|-------|------|-----|-----|-----|--|
| Father | A ₁ | CDe/CDe | MsNs | kk | a+ | — | — | | | |
| Mother | 0 | CDe/CDe | MsMs | kk | a+ | — | — | | | |
| BB - Twin A | A ₂ | CDe/CDe | MsMs | kk | a+ | — | — | | | |
| BB - Twin B | A ₂ | CDe/CDe | MsMs | kk | a+ | — | — | | | |
| | Hp | PGM | AP | Hb | G6PD | 6PGD | Cat | LHD | EsD | |
| Father | 2-2 | 2-1 | BB | A | B | N | N | N | 1-1 | |
| Mother | 2-1 | 1-1 | AB | A | B | N | N | N | 2-1 | |
| BB - Twin A | | 1-1 | BB | F | B | N | N | N | 1-1 | |
| BB - Twin B | | 1-1 | BB | F | B | N | N | N | 1-1 | |

Case 2 (BB-J)

Twins discordant for XXY were found on amniocentesis performed at 16 weeks gestation because of advanced maternal age. The 40-year-old mother had a pair of MZ twins in a previous marriage and there was a family history of twinning (Fig. 3). The parents were counseled about the effects of XXY, especially the wide variation of intellectual function, and about the associated gonadal failure. Options, including selective termination of the affected twin, were discussed and the parents opted to continue the pregnancy. The twins were born at 36 weeks with sizes appropriate for gestational age. The placentas were diamniotic, dichorionic. Karyotyping confirmed that one twin was 47,XXY and the other was 46,XY, and genotyping (Table 3) was consistent with dizygosity. Physical features of the affected twin are summarized in Table 1. It is notable that the unaffected twin has a slight pectus excavatum and one transverse palmar crease, while the affected twin does not. At this point, the parents do not wish to know which twin is affected.

TABLE 3 - Family 6802 - Genotyping

| | ABO | Rh | MNSs | Kell | Duffy | Jka | P |
|-------------|------------------|---------|------|------|-------|-----|---|
| Father | 0 | CDe/cde | MSMs | KK | a— | a— | — |
| Mother | A ₁ | CDe/CDe | NsNs | kk | a+ | a+ | + |
| BB - Twin A | A ₁ 0 | CDe/CDe | MsNs | Kk | a+ | a+ | — |
| BB - Twin B | A ₁ 0 | CDe/cde | MsNs | Kk | a— | a+ | — |

| | Hp | PGM | AP | Hb | G6PD | 6PGD | Cat | LHD | EsD |
|-------------|-----|-----|----|----|------|------|-----|-----|-----|
| Father | 1-1 | 1-1 | AB | A | B | N | N | N | 1-1 |
| Mother | 2-2 | 2-1 | AB | A | B | N | N | N | 1-1 |
| BB - Twin A | | 2-1 | BB | F | B | N | N | N | 1-1 |
| BB - Twin B | | 2-1 | AB | F | B | N | N | N | 1-1 |

DISCUSSION

Our results confirm previous reports of an association between twinning in families and occurrence of XXY [1,3,6,8]. More significantly, we have found an increased incidence of XXY among twins. This finding is interesting as it is the first time that the association of XXY and twinning has been assessed by ascertaining twins. The sample size of twins studied is small, however, and further study is indicated. The association may be due to a maternal age effect, since the indication for amniocentesis in the pregnancies was advanced maternal age, which is known to be related to an increased rate of both XXY and DZ twinning [4], but it may also indicate a causal relationship between carrying twins and conceiving XXY fetuses. It is also noteworthy that the mother of the affected MZ twins has autoimmune thyroid disease, as maternal thyroid antibodies have been implicated as a factor in chromosomal nondisjunction in trisomy 21 [2].

Examination of the phenotype in our patients confirms reports that most of the features of XXY do not become manifest until late childhood and adolescence [7]. In addition, it is apparent that the minor features of XXY, in particular simian creases and brachycephaly, are at best multifactorial in origin, since the MZ twins were discordant for these features.

There has been controversy about testicular pathology in fetuses with XXY. Murken et al [5] reported that the testes of a 20-week XXY fetus were grossly abnormal, showing hyperplasia of Leydig cells, hypoplastic and hypotrophic tubules, and decreased germinal epithelium. Gustavson et al [4] found no abnormalities in the histology of testes of a 17-week XXY fetus, when compared to age-matched controls. The finding of normal testicular histology for gestational age in our cases implies that dyshistogenetic testes are the exception rather than the rule in fetal XXY syndrome.

The second case demonstrated the difficult choice faced by parents when antenatal testing discloses twins discordant for a chromosomal disorder. The difficulty is especially prominent in a disorder like XXY, in which the effects are variable and not life-threatening. While one case is too limited an observation for generalization, it will be of great interest to see what the intellectual and psychologic development of the affected twin will be, free of the taint of labelling, with its possibility of self-fulfilling prophecy.

CONCLUSIONS

Our study of XXY fetuses ascertained in utero confirms an association of twinning and XXY. It appears that there may be a higher than normal incidence of XXY among male twins. Cytogenetic studies of a population of male twins by buccal smear examination would allow assessment of the true magnitude of this abnormality.

The fetal phenotype of XXY syndrome is not distinctly recognizable. In addition, it seems that there is no fetal testicular dyshistogenesis in XXY.

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