Twins in Sibships with Klinefelter's Syndrome

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Previous studies of Klinefelter's syndrome suggest that the frequency of twins in sibships might be relatively high. Ferguson-Smith (1958) studied the families of 4 patients with Klinefelter's syndrome, and found twins in the families of 3 of them, but the family relation was not stated. Mosier, Scott, and Cotter (1960) found twins in 2 of the sibships of 10 mentally deficient patients. One of the patients with Klinefelter's syndrome was a twin himself. The total number of sibs in the 10 sibships was, however, not mentioned. Among 9 cases of Klinefelter's, Maclean, Harnden, and Court-Brown (1961) found one who had a twin brother with normal chromosome pattern. Hoefnagel and Benirschke (1962) quote the above-mentioned results and other scattered findings of twins in families with the syndrome.

Materials and Methods

The study comprises 18 patients with chromatin-positive Klinefelter's syndrome, 11 of whom were found in a combined prevalence-incidence study of patients at a mental hospital comprising 1,160 patients. The diagnosis was made by sex-chromatin determination on Feulgen-stained buccal smears, and chromosome analysis was made on leucocyte cultures.

Results

In 5 of the 18 sibships, 6 twin births were found (Fig.): 4 twin pairs were dizygotic, but the zygosity was doubtful in 2 twin pairs. Of the 18 patients with Klinefelter's syndrome, 2 were twins themselves, one dizygotic, and the other of doubtful zygosity.

The total number of births in the 18 sibships was 111, and the total number of children 117, giving a twin birth frequency of 6 in 111 births or 5.4%, which is 3.4 times the twin birth frequency in the general population in Denmark during the years 1916-1920, which was 1.6% (Table I).

Mean maternal age for the 18 patients with Klinefelter's syndrome was 31.7 ± 8.7 , compared with mean maternal age in the general population in Denmark in 1916 of 29.7 (Table II). The year 1916 was chosen for maternal age comparison, as the mean age of the 18 patients with Klinefelter's syndrome in 1964 was 48 years.

Discussion

This finding correlates with the twin frequency in sibships of patients with Turner's syndrome.

TABLE I

PERCENTAGE OF TWIN BIRTHS IN MARRIED MOTHERS IN DENMARK DURING THE FIVE-YEAR PERIOD 1916-1920

Age-group	% of Twin Births
15-19	0.64
20-24	1.07
25-29	1.41
30-34	1.89
35-39	2.23
40-44	1.72
45-49	1.65
50-	0
Age unknown	1.95
Percentage, total	1.59

TABLE II

AGE DISTRIBUTION AT TIME OF BIRTH OF CHILD-BEARING MOTHERS IN DENMARK AND MOTHERS OF PATIENTS WITH KLINEFELTER'S SYNDROME

Age-group	Mothers of Patients with Klinefelter's Syndrome		Child-bearing Mothers in Denmark During 1916	
	Total	%	Total	%
15-19	1	5.6	1,250	2.0
20-24	3	16.7	12,640	19.9
25-29	5	27.8	19,041	30.0
30-34	2	11.1	15,833	25.0
35-39	4	22.2	10,263	16.2
40-44	2	11.1	4,056	6.4
45-50	1	5.6	342	0.5
Mean age		31.7 ± 8.7		29.7

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Fig. 1. Pedigrees of 5 families with twin births.

found by Nance and Uchida (1964) who studied the sibships of 34 cases of Turner's syndrome and found 8 twin births out of the total number of 128 births, giving a frequency of 6.3%.

Boyer, Ferguson-Smith, and Grumbach (1961) studied the sibships of 63 patients with Turner's syndrome and 236 births and found a twin birth frequency of 2.1%, and Lindsten (1963) found a twin birth frequency of 2.5% in 57 sibships with Turner's syndrome and 160 births. The pooled twin birth frequency in the three studies was 3.2%.

An increase in twin births in sibships with Klinefelter's syndrome might, to a certain extent, be explained by the fact that the frequency of twin births increases with the mother's age from a little below 1% in the age-group 15-19 to around 2% in the age-group 35-39 (Dahlberg, 1926). The percentage of twin births in Denmark during the years 1916-1920 is shown in Table I: it was 0.64 in the age-group 15-19, and 2.23 in the age-group 35-39. The increase in twin birth frequency with maternal age is, in practice due to an increase of dizygotic twins.

The frequency of Klinefelter's syndrome is probably also, to a certain extent, dependent on maternal age. Penrose (1961) studied 25 cases of Klinefelter's syndrome and found a mean maternal age of 30.8 ± 6.1 . The mean maternal age in the general population in England and Wales was 28.5. Ferguson-Smith, Mack, Ellis, Dickson, Sanger, and Race (1964) found a mean maternal age of 32.5 ± 6.7 in 45 cases of Klinefelter's syndrome.

In our 18 cases of Klinefelter's, we found a mean maternal age of 31.7 ± 8.7 , which is not statistically significantly higher than the maternal age of 29.7 in the general population in Denmark in 1916.

Table II shows that the distribution of maternal ages for the 18 patients with Klinefelter's syndrome is bimodal, as was also found by Penrose (1961). A bimodal distribution of maternal age in Klinefelter's syndrome might be expected if non-disjunction can be of paternal as well as maternal origin, and if maternal non-disjunction is dependent on maternal age and paternal non-disjunction independent of it, as suggested by the Xg studies in Klinefelter's syndrome made by Frøland,

Johnsen, Andresen, Dein, Sanger, and Race (1963) and Ferguson-Smith *et al.* (1964).

The mothers in sibships *a* and *b* were in their thirties when they had twins as well as a child with Klinefelter's syndrome. The mother of sibship *e* was in her forties when she had twins, and 50 years old when she had a son with Klinefelter's syndrome. In sibships *c* and *d* the maternal age for Klinefelter's syndrome was only 23 and 20. There might be a correlation between maternal age, twin births, and the births of sons with Klinefelter's syndrome in sibships *a*, *b*, and *e*, whereas such relation is not possible in sibships *c* and *d* with a maternal age of 23 and 20, respectively.

Further studies are needed before any conclusions can be drawn concerning a correlation between maternal age, twin frequency, and frequency of Klinefelter's syndrome.

If further studies of sibships with Klinefelter's syndrome and Turner's syndrome show a statistically significantly higher percentage of twins in such sibships, it would indicate a similarity in the mechanism of sex chromosome non-disjunction and of twinning.

Summary

Six pairs of twins were found in the sibships of 18 patients with Klinefelter's syndrome. There were 117 children and 111 births in the 18 sibships, giving a frequency of 5.4% twin births, which is 3.4 times the expected frequency in Denmark of 1.6%. The relation between a possible increased

maternal age in Klinefelter's syndrome and the increased twin birth frequency with increasing maternal age is discussed. It is concluded that if further studies show an increased frequency of twins in Klinefelter sibships, this would indicate a similarity in the mechanism of sex chromosome non-disjunction and of twinning.

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