A Variant Chromosome 17 in a Mother with Repeated Abortions and a 46,XY/47,XXY Klinefelter Son

K.-H. GUSTAVSON and B. KJESSLER

From the Department of Pediatrics, University Hospital, Umeå and the Department of Obstetrics and Gynecology, University Hospital, Uppsala, Sweden

ABSTRACT

A female with a satellited chromosome 17 is presented. She had suffered repeated abortions and later gave birth to a 46,XY/47,XXY Klinefelter boy. The significance of the variant chromosome 17 in the etiology of the mother's reproductive failure is discussed. The mental and physical development of her now 8-year-old 46,XY/47,XXY son has been checked regularly since birth. The boy showed a significant deviation in behaviour pattern and development of body habitus already from early infancy.

INTRODUCTION

The presence of a chromosomal aberration in either parent may lead to chromosomal non-disjunction during parental gametogenesis and thus give rise to aneuploid offspring (10).

This report presents a family with a mother who had suffered repeated miscarriages and who was found to be a carrier of a "satellited" chromosome 17. This woman was initially investigated because of infertility, and she eventually gave birth to a boy with an aberrant karyotype, 46, XY/47, XXY. The development during infancy of this now 8-year-old Klinefelter boy, was clearly deviant.

Family history and case records

(see pedigree, Fig. 1)

The index case (K. E. II:3) a healthy woman born in 1935, gave birth in 1962 to a phenotypically normal girl after an uneventful pregnancy. In 1965 and 1966 she had early spontaneous abortions of unknown etiology and was clinically investigated for her reproductive failure. No defects were found in her genital organs, and subsequently she again conceived and in 1969 gave birth to a boy (T. E. III:5) three weeks before term. The pregnancy and delivery were uneventful. The boy's birth weight was 2635 g, length 47 cm and skull circumference 32.5 cm. The infant showed slight clinical signs of prematurity.

The boy's mental and physical development since birth has been checked regularly by the same investigator (K.-H. G.). The gross motor development was somewhat slow; he sat without support at 9 months of age, crawled at 13 months, and walked alone at 17 months. However, his fine motor development was quite normal. Motor age examination and a Denver test at 10 months of age demonstrated an expected fine motor age of 10 months but a gross motor age of only 7 months. He was somewhat slow in learning to talk. The boy was still unable to talk distinctly at 4 years 7 months of age, and he still frequently reverses the sequence of syllables in words. At 6½ years of age developmental and intelligence tests were within the average range with higher performance scores than verbal scores. There was a slight delay in speech development, and moderate dyslexia. He was unusually easy and quiet as an infant. During the first 2 years of life he was extremely sensitive to sounds. He has always been calm, affectionate, and easy to manage, and he did not pass through any actual defiance period. He is still, at the age of 8 years, very dependent on his mother, and has little interest for, or contact with, other children. The family conditions have, however, been harmonious.

His height increased from 47 cm at birth (2 cm below the mean length for his gestational age) to 121 cm at 4½ years of age and to 138 cm at 6½ years of age (2 cm above +3 S.D. for his age); see Fig. 2. He weighed 23 kg at 4½ years of age. The body proportions have deviated since birth; at 1 year and 2 months of age his height was 82 cm with an upper-to-lower segment ratio of 0.96; span 85 cm. At 4 years his height was 116 cm, with an upper-to-lower segment ratio of 0.91; span 118 cm. His anterior fontanelle was closed at 17 months. The skull circumference at 4½ years was 51 cm (normal). His testes have always been small and soft and measured only 1.2 x 0.7 cm at 4½ years of age. Otherwise
I

II

III

Normal karyotype, female

Karyotype: 46,XX, 17 ps

Karyotype: 46,XY/47,XXY

Spontaneous abortion

Indicates the propositus

Fig. 1. Pedigree of the family.

he has been physically normal and has shown no external abnormalities (Fig. 3). The bone age was retarded about 2 months at a chronological age of 10 months as well as at a chronological age of 1 year 8 months, but it appeared normal at 6½ years of age.

**Chromosome studies**

Standard karyotypes as well as analyses of fluorescence stained chromosome preparations (Q-banding) were done on cultured leukocytes from peripheral blood.

**Special cytogenetic findings**

The mother II 3 (K. E.): In 83% of all cells analysed by conventional staining, one of the E-chromosomes (17 or 18) was found to have a distinct satellite-like structure at the terminal end of the short arm. The proximal part of the short arm was somewhat reduced in length, and the terminal “satellite structure” was clearly joined to the short arm of the chromosome by a faintly stained, but always clearly visible, “stalk” region (Fig. 4).

Quinacrine staining revealed two normal homologues No. 18 in the complement, but only one normal No. 17 could be recognized. The second No. 17 was replaced by a variant chromosome, with the regular banding pattern of a No. 17 chromosome in the long arm, but with only the most proximal part of the short arm displaying fluorescence. This could result from a marked secondary constriction...
in the short arm of the variant chromosome 17, i.e. 17 ph+. A more extensive structural rearrangement, e.g. a reciprocal translocation between a No. 17 and one of the acrocentric chromosomes, is a less likely explanation for the structural appearance of chromosome 17, since the fluorescent patterns of the rest of the chromosomes in the complement were quite normal. There was no close association of the variant chromosome 17 with any of the acrocentric chromosomes in groups D and G.

The specific variant chromosome 17 ph+ or 17 ps was not observed in the boy's grandmother (I:2), nor in the boy himself (III:5) or his sister (III:2). None of the proband's abortuses could be cytogenetically investigated.

The boy III:5 (T. E): Chromosomal analysis of cultured leukocytes from the boy was performed when he was only 4 days old because the mother was known to be a carrier of a structural chromosome variant. Two cell lines were observed in the boy: one with a 47, XXY complement (19 cells), and another with 46, XY (5 cells). Chromosome analyses of cultured leukocytes at 4½ years of age showed 47,XXY complement in 30 cells and 46,XY complement in one cell, and at 6½ years of age all 30 cultured leukocytes had a 47,XXY complement. X-chromatin investigation of cells from buccal smears at 10 months of age showed one X-chromatin body in 24% of the cells analysed: 3% of his neutrophil leukocytes had drumsticks.

DISCUSSION

Satellited chromosomes presumed to be No. 17 have been reported by several investigators. Such variant chromosomes have been shown to represent a heritable trait without apparent phenotypical effects (2, 6, 12, 15, 17, 20).

Sandström & Jenkins (13) reported a family with a 17p marker chromosome, segregating in four generations, which was identified by Quinacrine staining. The morphology of their 17p marker chromosome appears similar to the morphology of our presently reported chromosome 17ph+.

Nevertheless, including the present family, at least three instances are known where parents (one or both) heterozygous for this type of variant chromosomes 17 have had aneuploid offspring (2, 15). This observed association may be fortuitous, because of ascertainment bias. However, the present index case (the mother) was investigated because of reproductive failure, and her variant chromosome 17 was demonstrated before she had given birth to her XY/XXY son.

The structural variation per se of this variant chromosome No. 17 does not seem to be related to the phenotype of its carrier, and it is uncertain whether in the present family it was related to the reproductive failure of the mother. However, Mikkelson (14) found a significantly higher number of autosomal variants in parents of 21-trisomic children than in randomly selected men and women. The presence of a variant autosome in the complement together with an increased maternal age in the present index case may thus both have been predisposing factors for meiotic irregularities and subsequent conception of an aneuploid offspring.

Both the physical and mental development of the present aneuploid, XY/XXY boy present some interesting features. Eight of the ten Klinefelter boys in the series of Annell et al. (1) had an unusually tall stature as also had the majority of the boys with Klinefelter's syndrome in the series reported by Schibler et al. (19). It is of interest that the height increment of the boy in our family was abnormally large even during his first 18 months of life, and that since the age of 3 years his height has lain outside +3 S.D. Relatively long legs and a diminished upper-to-lower segment ratio are evident in schoolboys with the XXY syndrome (3, 19). The present subject demonstrated that these skeletal disproportions may be recognized even earlier in life, since he had relatively long legs with a low upper-to-lower segment ratio already as an infant. Small testes is a usual finding in prepubertal XXY boys (1). The testes of our XY/XXY boy have been
small since birth, which indicates primarily decreased total mass of germinal cells.

Behavioral and psychiatric disturbances are often present in Klinefelter subjects long before puberty. As in the present case, such boys (XXY as well as XY/XXY subjects) are usually very easy to deal with at pre-school age, quiet, passive and affectionate (8, 21). They usually do not undergo any clear defiance period, and they seem to be very dependent on their mothers. Most of them, like the present patient, have been noted to be late in speech development (21). In many cases the significant social problems begin with marked difficulties in learning and adjusting, and problems concerning relations to other children are notified when these patients start school (1, 9, 16).

The presence of an extra X chromosome in a significant proportion of cells in males therefore indeed seems to affect the physical body proportions as well as the behaviour pattern of the carrier even very early in life.

ACKNOWLEDGEMENTS
This investigation was supported by grants from the Swedish Medical Research Council (No. 17X-2020) and the Prenatal Research Fund sponsored by the Stockholm Newspaper Expressen.

REFERENCES

Received November 19, 1977

Address for reprints:
K.-H. Gustavson, M.D.
Department of Pediatrics
University Hospital
S-901 85 Umeå
Sweden

Upsala J Med Sci 83