

47,XXY (KLINEFELTER SYNDROME) AND 47,XYY: ESTIMATED RATES OF AND INDICATION FOR POSTNATAL DIAGNOSIS WITH IMPLICATIONS FOR PRENATAL COUNSELLING

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SUMMARY

Cytogenetic surveys of neonates have found that approximately one boy in 500 is born with an extra sex chromosome. Some of these boys are now being diagnosed when prenatal karyotyping is done for the detection of Down syndrome and other major aneuploidies. This study estimates what proportion of those not detected prenatally will be diagnosed postnatally and what the indications for karyotyping are likely to be. We ascertained all 47,XXY and 47,XYY males detected prenatally and postnatally (during the 4 years 1990–1993) in the three cytogenetic laboratories in the North Thames (West) region. The age at diagnosis and indication for karyotyping were noted for cases diagnosed postnatally. Less than 10 per cent of the estimated number of affected fetuses were detected prenatally. This study suggests that most males born with these chromosome patterns will go through life without being karyotyped, that the commonest indication for a 47,XYY male to be karyotyped will be developmental delay and/or behaviour problems, and that the commonest indication for a Klinefelter male to be karyotyped will be hypogonadism and/or infertility. It would appear that most undiagnosed 47,XXY and 47,XYY males do not look or behave in a manner which prompts testing for a chromosome abnormality. © 1977 by John Wiley & Sons, Ltd.

KEY WORDS: Klinefelter syndrome; 47,XXY; 47,XYY; sex chromosome abnormalities

INTRODUCTION

Since 1 January 1990, the three cytogenetic laboratories in the North Thames (West) Health region have been reporting to the Regional Congenital Malformation Register abnormal karyotypes found both prenatally and postnatally. Among those cases reported are all male fetuses or babies in whom either a 47,XXY or a 47,XYY

karyotype is detected. The first four years' (1990–1993) data showed that in about half of those cases of 47,XXY and 47,XYY diagnosed prenatally, the mother had a termination of pregnancy. Presumably this was because of fears about how the condition in question would manifest itself. This study examines one aspect of the question of what might happen to those boys who were born undiagnosed.

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Population studies (Bochkov *et al.*, 1974; Buckton *et al.*, 1980; Friedrich and Nielson, 1973; Hamerton *et al.*, 1975; Hansteen *et al.*, 1982; Hook, 1992; Jacobs *et al.*, 1974; Kuleshov *et al.*, 1978; Lubs and Ruddle, 1970; Maeda *et al.*, 1991; Nielsen and Sillescu, 1975; Ratcliffe *et al.*, 1990;

Sergovich *et al.*, 1969; Walzer and Gerald, 1977) show that approximately 1 in 800 males has Klinefelter syndrome, a 47,XXY karyotype-male with an extra X chromosome. While such males are invariably infertile, it is possible that they will have no other problems associated with the condition. However, some of them will have problems associated with low levels of testosterone, such as hypogonadism. The average IQ for Klinefelter boys is 10-15 points lower than for boys with the more usual 46,XY karyotype and they are more likely than other boys to require extra educational help or speech therapy (Cohen and Durham, 1985; Nielson and Pelsen, 1987; Nielsen and Wohlert, 1990; Ratcliffe *et al.*, 1990; Sorensen, 1992).

About 1 in 1000 males has a 47,XYY karyotype-male with an extra Y chromosome. Many such males have no noticeable problems caused by the extra Y chromosome. However, like the boys with 47,XXY, the average IQ may be 10-15 points below that of 46,XY boys and they are more likely than other boys to require extra educational help. They are also more likely to exhibit behaviour problems (Cohen and Durham, 1985; Nielsen and Wohlert, 1990; Ratcliffe *et al.*, 1990).

METHOD

This study includes all cases of 47,XXY and 47,XYY diagnosed in the three laboratories in the North Thames (West) region (The Kennedy-Galton Centre, St Mary's Hospital, and Queen Charlotte's and Chelsea Hospital) in the 4 years 1990-1993. The babies and fetuses were ascertained from the North Thames (West) Congenital Malformation Register. In addition, staff at the three laboratories reported all cases of these conditions found in males of any age during those 4 years. To ensure that we did not miss cases referred to a specialist children's centre in North Thames (East), we also checked with the main cytogenetic laboratory in that region but did not find any cases of North Thames (West) residents.

Knowledge of the incidence of 47,XXY and 47,XYY from surveys of newborns enables us to estimate approximately how many males in a given population are affected with the syndromes. The size of the male population in this study was presumed to be half the number of all babies born in hospitals in the region during the study period;

this is a slight underestimate since there are slightly more males born than females.

In order to estimate the numbers of Klinefelter and 47,XYY boys born during the 4 years who will be diagnosed later, the study includes males of any age who were diagnosed during that time. Thus, boys from the past are serving as proxies for today's boys in the future. This should be a legitimate substitution as long as one bears in mind the fact that the number of births in the region has increased over the years (there were 6 per cent fewer births in 1980 than in 1990 to residents in the region) (P. Crow, Office of National Statistics, personal communication), so the proxy population for the older age groups will contain slightly fewer Klinefelter and XYY males than our actual population will when it reaches that age. However, this is at least partially compensated for by the fact that fewer pregnancies were subjected to prenatal diagnosis in the past, so a higher proportion of boys with sex chromosome abnormalities were born without having been detected prenatally. This method of using proxies also makes the assumption that 47,XXY and 47,XYY males are no more or less likely to move in and out or to be karyotyped in or out of the region than are 46,XY males.

Two of the three laboratories were able to supply the numbers of 46,XY males who were karyotyped during the period 1990-1993 and the reasons for karyotyping them. This allows the figures for the 47,XXY and 47,XYY males to be viewed in context.

RESULTS

Factors which caused us to overestimate the numbers of undiagnosed affected males (changes in numbers of births) are balanced by others which caused underestimation of numbers (sex ratio and increase in amniocentesis rates). However, the numbers of undiagnosed cases in both the newborn and the proxy populations are only estimates, so we have not done detailed statistical analysis. The word 'significant' is used in the text only once when the difference would remain highly significant even if our figures grossly exaggerated the real difference.

The vast majority of boys with Klinefelter syndrome were not diagnosed prenatally (Table I). This is because amniocentesis was done either for advanced maternal age, and the maternal age effect is weaker for Klinefelter syndrome than for Down syndrome (Hook, 1981), or for a high-risk serum

Table I-Klinefelter males—estimated number born

	Babies born in units in region	Estimated number of males	Estimated number of 47,XXY males	Number of 47,XXY males diagnosed prenatally	Estimated number not diagnosed prenatally
1990-1993	198 095	94 547	118	12	106

Table II-Klinefelter males not diagnosed prenatally ($n=106$): ages diagnosed postnatally

	Diagnosed under 1 year	Diagnosed 1-10 years	Diagnosed 11-20 years	Diagnosed more than 20 years	Total diagnosed postnatally
1990-1993	1 (1%)	0	6+1* (7%)	19+1* (19%)	28 (26%)

*46,XY/47,XXY mosaics.

Table III-Klinefelter males-indication for postnatal karyotyping

Age at karyotyping	Developmental delay	Behaviour problems	Hypogonadism and/or gynaecomastia	Infertility	Other/unknown	Total
<1 year					1	1
1-10 years					0	0
>20 years	4	1	11	5	11	207
Total	4	1	10	5	8	28

screening result or abnormal ultrasound findings (neither of which would indicate a high risk for Klinefelter syndrome). If the diagnosis was not made prenatally, it was very unlikely to be made during the first decade of life, and nearly three-quarters of the estimated cases were never diagnosed in the proxy population (Table II). Most males who were diagnosed were karyotyped because of hypogonadism or infertility (Table III).

The vast majority of boys with 47,XXY were not identified prenatally (Table IV). This is because those pregnancies in which an amniocentesis is done are not at increased risk for 47,XXY. There is not a maternal age effect for 47,XXY, and a high risk for an affected pregnancy would not be predicted by a high-risk serum screening result or abnormal scan findings. Only 12 per cent of the estimated proxies were eventually diagnosed

(Table V). Half of those diagnosed were karyotyped because of developmental delay and/or behaviour problems during the first decade (Table VI).

Tables VII and VIII list cases from two of the laboratories only and exclude men karyotyped due to their partner having repeated miscarriages or their child having an abnormality, since Klinefelter men would never be in that situation. Table VII shows that during the first decade of life, a Klinefelter boy in the proxy population was no more likely to be karyotyped than was a 46,XY boy. During the first decade of life, a 47,XXY boy was more likely to be karyotyped than either a Klinefelter or a chromosomally normal boy. During adolescence and after, Klinefelter boys and men were significantly more likely to be karyotyped than were chromosomally normal boys and

Table IV—47,XYY males—estimated number born

	Babies born in units in region	Estimated number of males	Estimated number of 47,XYY males	Number of 47,XYY males diagnosed prenatally	Estimated number not diagnosed prenatally
1990-1993	198 095	94 547	94	3+2*	89

*46,XY/47,XYY mosaic and 47,XYY/45,X mosaic.

Table V—47,XYY males not diagnosed prenatally ($n=89$): ages diagnosed postnatally

	Diagnosed under 1 year	Diagnosed 1-10 years	Diagnosed 1 1-20 years	Diagnosed more than 20 years	Total diagnosed postnatally
1990-1993	1 (1%)	4 (4%)	1 (1%)	5 (6%)	11 (12%)

Table VI—47,XYY males-indication for postnatal karyotyping

Age at karyotyping	Developmental delay	Behaviour problems	Infertility	Trans-sexual	Dysmorphic	Total
<1 year					1	1
1-10 years	4					4
1 1-20 years	1					1
>20 years		1	2	2		5
Total	5	1	2	2	1	11

Table VII-Postnatal diagnosis of males with 46,XY, 47,XXY and 47,XYY karyotypes at two, laboratories (1990-1993)

Karyotype	Diagnosed <1 year	Diagnosed 1-10 years	Diagnosed 1 1-20 years	Diagnosed >20 years	Total diagnosed postnatally
46,XY	461	706	147	246	1560
47,XXY	1	0	7	18	26
47,xYY	1	4	1	3	9

Excludes males karyotyped because of partner's abnormal pregnancy outcome.

men, while 47,XYY boys and men were slightly more likely to be karyotyped than were 46,XY boys and men. One puzzle is why more Klinefelter men were not diagnosed following infertility investigations. This study is not able to shed any light on that question. Further research is needed to explain whether these men are being seen in infer-

tility clinics but not being karyotyped, or whether they are not being investigated for infertility at all. If they are not being referred for tests, is this because a large proportion of them are not attempting to become fathers?

Table VIII compares the indications for karyotyping boys and men who were subsequently found

Table VIII-Indication for karyotyping of 46,XY, 47,XXY and 47,XYY males at two laboratories (1990-1993)

Karyotype	Developmental delay	Behaviour problems	Malformation	Infertility	Abnormalities in sexual development*	Other not specified	Total
46,XY	1100		370	10	80		1560
47,XXY	4	1		4	9	7	25
47,XYY	5				2	2	9

*Abnormalities of sexual development include both hypogonadism/gynaecomastia and psychosexual development. Excludes males karyotyped because of partner's abnormal pregnancy outcome.

to have normal karyotypes, Klinefelter syndrome, and 47,XYY. The commonest reason for a chromosomally normal or a 47,XYY individual to be karyotyped was developmental delay, whereas for the 47,XXY male, the commonest indication for karyotyping was infertility or hypogonadism.

DISCUSSION

With increasing numbers of pregnancies being subjected to prenatal karyotyping because of abnormal ultrasound findings and high-risk serum screening results, it is inevitable that a larger proportion of fetuses with sex chromosome aneuploidy will be detected prenatally as an incidental finding. Our research infers that in the past, many individuals with these karyotypes would have gone through life undetected. The chance prenatal diagnosis of a boy with XXY or XYY presents parents with a difficult dilemma, and many professionals involved in prenatal diagnosis say that sex chromosome aneuploidies are the ones they dread the most. The prognosis is relatively good but the knowledge that the abnormality exists may make the parents feel unable to continue with the pregnancy. Parents worry about problems that the child might possibly have even if it is more likely that he would not. Having been told that the child has a chromosome abnormality, they may also view the problem as greater than the sum of its parts. For example, how many women would terminate a pregnancy if they were told that the baby would have an IQ 10 or 15 points lower than his brother and that he would be infertile-without any mention being made of a chromosome abnormality or a syndrome? We do not know the answer to this question.

When couples are faced with the dilemma of what to do in the face of a prenatal diagnosis of 47,XXY or 47,XYY, some of them turn to out-of-date literature on the subject which is affected by ascertainment bias: only those boys who are most affected by their condition will be identified in childhood (Garrett and Carlton, 1994). Doctors' views are also coloured by ascertainment bias; they see the 47,XXY and 47,XYY boys and men who have severe problems. The natural tendency is to assume that the problems are due to the abnormal karyotype-something which cannot be done when the karyotype is normal.

While it is important for couples facing this dilemma to be aware of both definite and possible problems associated with the syndromes, it is also important for them to see these problems in context. For example, when they are given the chance of the boy being developmentally delayed, this needs to be compared with the chance of a chromosomally normal male being developmentally delayed. There is a tendency among both professionals and parents to compare problems that a child might have with problems that a 'perfect' child would have, and, by definition, the perfect child would have no problems. However, this 'perfect' child does not exist; parents and professionals alike should compare a child who is likely to have specific problems with a 'normal', and therefore imperfect, child.

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