

Is the prevalence of Klinefelter's syndrome increasing?

An abridged version by Povl Larsen of a paper by Joan K Morris[†], Eva Alberman[†], Claire Scott*, Patricia Jacobs[°] – which was the basis for Dr Jacobs presentation at the KSA Conference 2007

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INTRODUCTION

Information on the prevalence of sex chromosome trisomies is based on six large surveys of consecutive newborns carried out in the late 1960s and early 1970s. All three sex chromosome trisomies had a similar live birth prevalence of 1 per 1000 same sex births. However, recent data from the UK Chromosome Abnormality Database showed a much greater number of prenatal diagnosis of XXY (Klinefelter's syndrome) than either XXX (Triple X) or XYY.

The excess of XXY prenatal diagnoses could be explained either by much greater fetal losses occurring in XXY, than in XXX or XYY pregnancies between the time of prenatal diagnosis and birth or by an increase in the prevalence, possibly due to the increases in maternal age that have occurred since the 1970's. If the latter were the case this should also apply to XXX pregnancies, which like XXY pregnancies increase in prevalence with maternal age. In this paper, the authors collated evidence on the prevalence of XYY, XXY and XXX from studies on series of newborns, spontaneous fetal and perinatal deaths and prenatal diagnoses to determine an explanation for the greater numbers of XXY prenatal diagnoses observed.

DISCUSSION

The greater number of prenatal diagnoses of XXY than either XXX or XYY reported in the UK Chromosome Abnormality Database is consistent with their prevalence at birth after the early 1970s referred to as the "later newborn surveys" and data on spontaneous abortions and perinatal deaths. Comparing the later newborn surveys with the original newborn surveys carried out in the late 1960s and early 1970s demonstrated increased birth prevalence of XXYS, but not of XYYs or of XXXs. While the apparent increase in XXY might be the result of errors in the early newborn surveys, there is no plausible reason why the XXYS but not the XXXs or XYYs would have been underestimated. Furthermore, the prevalence of XXYS is very consistent among the six surveys.

During the period of the early newborn series, there were no pre-natal diagnoses and thus no selective abortions of chromosome abnormalities. In contrast, during the period of the later newborn surveys prenatal diagnosis was introduced resulting in selective termination of some chromosomally abnormal fetuses. Data from the Wessex region between 1976 and 2005 indicates that XXYS were almost twice as likely to be selectively aborted as either XXXs or XYYs. Therefore, if these data are representative of other jurisdictions, selective abortions of XXX or XYY pregnancies could not explain the relative excess of XXY

pregnancies in the later newborn series. This relative excess could also not be explained by any changes in ascertainment due to improvements in technology, which would be expected to affect all three sex chromosome trisomies equally.

It seems unlikely that the proportion of sex chromosome trisomy conceptions that spontaneously abort has changed since 1960, and therefore the higher prevalence in the later birth surveys suggests that there was a higher prevalence at conception of XXYs than at the time of the earlier surveys.

Studies of parental origin have found that around 50% of XXYs are maternal and 50% paternal in origin. Maternal non-disjunction (the sex chromosomes failing to separate) results in an ovum with two X chromosomes, which theoretically is equally likely to be fertilised by an X or a Y bearing sperm resulting in an equal frequency of XXY and XXX conceptions of maternal origin. Therefore if the increase in XXY was due to maternal non-disjunction, associated with increasing maternal age, a similar increase should have been observed in the XXX conceptions as 95% of them are maternal in origin (May, et al, 1990). This was not seen.

The XXYs of paternal origin result from non-disjunction (the sex chromosomes failing to separate) of the XY bivalent during paternal MI (Thomas, et al 2000), whereas virtually all XYYs result from non-disjunction (the sex chromosomes failing to separate) at paternal MII (Robinson & Jacobs, 1999). Therefore, a possible explanation for the increased prevalence of XXYs compared to XYYs is an increase in the frequency of non-disjunction of the paternal sex chromosomes in the MI division of spermatogenesis. A number of factors have been reported that interfere with pairing, recombination or the detection of errors in these processes whose action is restricted to MI (Hunt & Hassold, 2002). Such factors would be expected to be associated with XY non-disjunction but not YY non-disjunction, which happens at MII (Robinson & Jacobs, 1999).

CONCLUSION

The authors speculate that the apparent increase in XXY males, if caused by an increase in errors in paternal MI, may result from the same factors, presumably environmental, that are associated with the well-documented fall in sperm count in our species (Andersen, et al, 2000; Ervine, et al, 1996; Carlsen, et al, 1992).

There are two observations that lend some to support this suggestion. The frequency of aneuploidy (an unusual number of chromosomes) in sperm, studied using FISH technology, (Hassold, 1998) has shown 1% of sperm to be hyperhaploid in normal males and the sex chromosomes to be the most frequently involved. Secondly, when the frequency of hyperhaploidy in sperm from men with a low sperm count is examined the majority show an increase in disomic sperm, which is especially marked for the sex chromosomes. Martin et al (1998) compared hyperhaploidy in males with mild, moderate and severe oligospermia (low sperm count) and found an increase in sex chromosome aneuploidy (an unusual number of chromosomes) as the sperm count fell.

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