Long term outcome in children of sex chromosome abnormalities

Shirley Ratcliffe

An unduly pessimistic description of what it means to have an extra X or Y chromosome is frequently given to the parents of an affected fetus or child by geneticists and paediatricians because the source of their information has been biased towards abnormality. In 1967 the Medical Research Council set up a cytogenetic survey of consecutive newborn infants to establish the incidence of the various chromosome abnormalities. The long term follow up of children with sex chromosome abnormalities ascertained in the survey, which screened 34,380 newborns in Edinburgh between 1967 and 1979, has enabled a more balanced prognosis to be reached.

Most boys with the karyotypes 47,XXY and 47,XYy and girls with 47,XXX are never diagnosed. While that may suggest that the conditions are of no importance to the affected individuals, I will show using the following results that this is not the case.

Based on the incidence at birth obtained from cytogenetic surveys of around 200,000 infants from the UK, Denmark, Canada, the USA, and Japan, an XXY karyotype was found in 1.3 per 1000 male infants, while XYY and XXX occurred with a frequency of 1 per 1000 male or female infants, respectively. Using these incidence figures Abramsky and Chapelle found that 10% of expected cases of XYY boys were identified at amniocentesis, a further 26% were diagnosed in childhood or adult life on account of hypogonadism, gynaecomastia, infertility, or developmental delay, leaving 64% undiagnosed. Among XYY boys, where there is no advanced paternal age effect, 85% were calculated to be undiagnosed either before or after birth. Abramsky and Chapelle did not include XXX females, but an estimate can be made from the maternal age distribution of 57 affected newborns where 26% were born to mothers over the age of 35 years. It is reasonable to expect that these would now be diagnosed at amniocentesis, but as these girls have no characteristic physical features the remaining 74% probably remain undiagnosed.

Follow up of 53 cases of sex chromosome abnormalities in the three main categories identified in the Edinburgh survey continued until the end of 1995 with participation of 93% of the cases, together with a control group of 94 boys and 75 girls from the same population. At six monthly visits to the growth clinic a protocol of assessments of health, growth, and development were completed; the psychologist attached to the study was not informed of the karyotype. The growth studies were carried out using the methods and equipment devised by Professor J M Tanner after I had undertaken training at the Institute of Child Health in London. No invasive procedures were done, hormone assays being carried out on urine or saliva.

The parents of children with XXY and XXX karyotypes were given as much information as was then available about their conditions, with the explanation that the purpose of the study was to provide a clearer picture of the whole condition. However, the likely infertility of XXY males was not mentioned at the beginning in order not to disturb the parents’ perception of the child’s masculinity. For the XYY infants, in view of the much publicised association with criminality at the time the survey started, the Medical Research Council’s policy was that the information should be discussed first with the general practitioner, then passed on to the parents only if it was considered that it would be helpful to them in handling the child.

47,XXY

One child with 47,XXY karyotype died of renal agenesis, otherwise no congenital malformations were detected. The surviving 19 boys in this group were studied from birth until the ages of 16 to 27, except for one boy who joined the study at age 5 years. The social class distribution differed from that of the Scottish population with 44% in social class I and II (professional and skilled); this shift in distribution was also observed in the original group of nine XXY men identified in the maximal security hospital at Carstairs, Scotland in 1965.

GROWTH

Size at birth did not differ from that of the controls in terms of birth weight, length or head circumference; however, the velocity of growth increased significantly from age 2 years continuing throughout childhood, so that by the onset of puberty the average XYY boy was 7.6 cm taller than the controls at 151 cm. The pubertal growth spurt was longer and of longer duration resulting in a final height of 188 cm with retention of the father–son correlation in...
Sex chromosome abnormalities

height \( (r = 0.72) \). Onset of sexual development was six months later than in the controls but thereafter proceeded normally.

NEUROLOGICAL FINDINGS

Neurological examination revealed intention tremors of the hands in two boys, and involuntary grimaces of the face in two others. Additionally, a quantified test for fine motor coordination produced a score of \(-1.29\) SD compared with controls, and \(-1.42\) SD for balance, indicating subtle neurological impairment.

PSYCHOLOGICAL DEVELOPMENT

In early childhood the XYY boys were more active and ate and slept better than controls. However, they had more temper tantrums in response to frustration.\(^3\) One source of this was the child's difficulty in communication; 42% had delayed speech development compared with 18% of the male controls.

INTELLIGENCE TESTS

Assessment of their cognitive ability using the Wechsler intelligence scale for children (WISC) revealed a small but significant lowering of scores for the XYY boys compared with social class matched controls (verbal 99.7 vs 114.4, performance 104.3 vs 115). Although the numbers in each cell were small, the usual social class gradient in intelligence quotient (IQ) was maintained, and comparison with siblings' IQ scores confirmed the small deficit.\(^1\) Similar results were obtained for 11 XYY boys in Boston.\(^9\)

Difficulty in learning to read was identified by the school teachers (who were not aware of the karyotype) in 54% of the XYY boys compared with 18% of the controls, and remedial help was given. There was no significant deficit in mathematical ability. On leaving school two boys gained acceptance to university courses in engineering and three attended technical colleges.

BEHAVIOUR

The behaviour of many of the XYY boys caused problems for their parents as reflected in the responses to the Rutter parental questionnaire\(^9\) where the total score and the antisocial score were significantly raised. Wechsler intelligence scale for children (WISC) revealed a small but significant lower-

INTELLIGENCE TESTS

Assessment of their cognitive ability using the Wechsler intelligence scale for children (WISC) revealed a small but significant lowering of scores for the XYY boys compared with social class matched controls (verbal 99.7 vs 114.4, performance 104.3 vs 115). Although the numbers in each cell were small, the usual social class gradient in intelligence quotient (IQ) was maintained, and comparison with siblings' IQ scores confirmed the small deficit.\(^1\) Similar results were obtained for 11 XYY boys in Boston.\(^9\)

Difficulty in learning to read was identified by the school teachers (who were not aware of the karyotype) in 54% of the XYY boys compared with 18% of the controls, and remedial help was given. There was no significant deficit in mathematical ability. On leaving school two boys gained acceptance to university courses in engineering and three attended technical colleges.

47,XY

The 19 47,XY boys seen for follow up had a normal social class distribution, and DNA studies showed the additional X chromosome to be of maternal origin in 11 (mean maternal age 30.5 years) and paternal in eight (mean maternal age 27.1 years). Two boys had congenital malformations (talipes equinovarus and pectus excavatum), in addition the testes were undescended in three and subsequent ascent occurred in four resulting in surgery in 37% of the XYY boys compared with 1% of the controls.

GROWTH

At birth the XYY infants were smaller in weight, length, and head circumference than the controls, and head circumference remained between the 10th and 25th centiles reflecting a small adverse effect on brain growth,\(^11\) found also in our study of 12 XXY youths from a sex chromatin survey of newborns in 1959–62.\(^12\) During childhood there was a notable increase in height velocity between 5 and 8 years of age owing to greater leg growth, but the magnitude and timing of the pubertal growth spurt did not differ from the controls, with a final height of 186 cm.\(^11\) A tendency to central obesity was observed in 75% of the XYY boys with skinfold thickness exceeding that of the controls from 6 years of age.

SEXUAL DEVELOPMENT

At birth a minority of the XXY infants had underdevelopment of the penis and there was a good response to local (2% testosterone cream) or systemic (single injection of 25 mg testosterone enanthate) treatment. The testes were initially normal in size and consistency but failed to grow normally. At the onset of puberty at 11.9 years the testes enlarged to around only 5 ml volume, except for two cases in which there was enlargement to 12 ml followed by
involution. By the end of puberty the penis was of normal size in 77%, and pubic hair had progressed to Tanner stage 6 in 10 boys. Gynaecomastia was observed in 56% but was transient in most, lasting one to three years: it was also noted in 36% of the controls. One XXY boy had bilateral mastectomies performed by a plastic surgeon with excellent results.

HORMONE STUDIES
Prenatal testosterone in XXY fetuses were measured in amniotic fluid and did not differ from XY fetuses. The postnatal surge in testosterone also occurred in XXY infants with a comparable peak concentration to that of controls. Similarly, during childhood testosterone concentrations in saliva were normal and started to rise at the onset of puberty, but by age 16 they were significantly lower than in controls and gonadotrophin became raised six months after the onset of puberty.

PSYCHOLOGICAL DEVELOPMENT
Delayed speech development was more common in XXY cases, with 42% having speech therapy. The mean WISC verbal scores of 94.3 (range 65 to 129) and performance 97.6 (range 75 to 128) were significantly lower than controls and siblings and, as before, the social class gradient was preserved. These findings are in agreement with other population based studies in children and adults. Mathematical ability was also significantly poorer, as was short and long term memory. However, the two boys with the highest IQ scores obtained university degrees. In 1972 Becker recorded that among his endocrine clinic series of 104 men with Klinefelter syndrome there were physicians, engineers, ministers, and accountants.

BEHAVIOUR AND PERSONALITY
At the age of 3 years the behaviour rating questionnaire showed that the XXY boys had difficulties in relationships with peers and siblings and this remained a problem throughout childhood. Most boys were quiet and unassertive, disliking rough games and being easily moved to tears when bullied by other children. On the Rutter parental questionnaire at age 11–15 they had a raised total score for problems, but differed from the XYY boys in that it was the neurotic score that was higher, not the antisocial score. The rate of psychiatric referral at 26% was higher than for controls (9%) but lower than for the XYY boys. During adolescence and early adulthood there was no increase in the percentage with convictions compared with the controls.

SEXUALITY AND FERTILITY
None of the 19 boys in this study, or the 12 boys from the sex chromatin survey had homosexual preferences, while two of the control boys did. The small testicular volume makes it likely that the XXY young men will be infertile, but in view of the report of proved fertility in a non-mosaic XXY man it is necessary to have the results of several sperm counts before making definitive statements about any XXY man’s fertility. The oldest of the XXY men in this study has married and his wife became pregnant with the aid of donor sperm.

EMPLOYMENT
While most XXY boys have less skilled jobs than their fathers, and experienced more job changes, there was no increase in unemployment.

47,XXX
The 16 girls in the 47,XXX group ranged in age from 16 to 27 and had a normal social class distribution. Three had congenital malformations: horseshoe kidney, patent ductus arteriosus, and congenital dislocation of the hips.

GROWTH
The birth weight, length, and head circumference were all significantly smaller than in the female controls. Head circumference at birth and at 7 years correlated significantly with later IQ scores, and despite a normal growth velocity postnatally, brain size remained smaller and the mean head circumference was around the 10th centile. As for the XXY boys, height velocity increased during mid-childhood owing to greater leg growth. The pubertal growth spurt was of normal magnitude but its timing was six months later than for the control girls, as was the age of menarche.

PSYCHOLOGICAL DEVELOPMENT
Speech development was delayed in 50% of the XXX cases, and IQ scores were significantly lower than in female controls and siblings, with a mean verbal score of 85.3 (range 67 to 109) and performance score of 88.3 (range 67 to 110). As in the boys with sex chromosome abnormalities the social class gradient was maintained—for example, the XXX girl with an IQ of 110 had parents who were both university graduates. These results are in close agreement with those from 11 XXX girls in Denver and Toronto.

All girls except one attended normal schools but experienced learning problems and required remedial teaching for reading and mathematics. Three girls proceeded to further education in arts related subjects. An excess of behaviour problems was evident at age 3 and 11; four XXX girls (25%) had psychiatric referral compared with 3% of the female controls. The diagnoses included depression, drug abuse, and obsessive–compulsive disorder.

Most XXX girls expressed relief at leaving school where they felt under pressure, and they gained employment in hairdressing, cooking, and waitressing, while four became housewives. They were physically attractive girls and they displayed a common sense attitude that counterbalanced their low educational achievements. In general their outcome was more successful than that described for the 11 XXX girls from Denver.
Conclusions
An additional X or Y chromosome has a mild adverse effect on brain development, most noticeable in the former case for girls, while the gonadal effect is severe in boys and questionable in girls. Review of the literature reveals that 16% of the offspring of XXX women have chromosomally abnormalities but this figure is inevitably affected by the tendency to report abnormality, and results from the cohort described here will require another 10 years of observation to be of use; therefore, it is advisable for XXX women to have amniocentesis in early pregnancy.

For XXY men, once infertility is established it is important to emphasise that family life is not precluded — supplementary testosterone will maintain libido, donor sperm can enable pregnancy with full confidentiality, and in the future intracytoplasmic sperm injection may be possible if some sperm are being produced.

Boys and girls with an extra X chromosome have a high risk of educational difficulty, and regular assessment of educational achievements will allow early intervention and help prevent secondary behavioural problems. In contrast to the findings from surveys of institutions we did not find evidence of increased criminality in XXY cases, but our numbers are small and the results from the other newborn surveys are awaited.

In the XYY boy, the combination of lowered intelligence, delayed development of speech, and emotional maturity, together with greater body size leading to higher expectations, combine to increase the frequency of behavioural problems and of criminal conviction. There is however improvement with time in spontaneous maturation, educational intervention, consistent parental management, and psychiatric help when necessary.

To reduce the number of children with sex chromosome abnormalities who remain undiagnosed it would be advisable to include sex chromat screening, or chromosome analysis, in the investigation of all boys with undescended testes, as an XXY karyotype is three times greater in these boys than the population rate. Similarly, all boys with micropenis or gynecomastia require chromosome analysis.

Prepubertally, a combination of height at or above the 75th centile, owing to increased leg length, and a head circumference around the 15th centile, with truncal obesity and educational difficulties, strongly suggest an XXY karyotype.

The combination of tall stature with behaviour problems from early childhood are suggestive of an XXY constitution, but the influence of paternal height must be borne in mind as the XXY son of a short father may be of average height.

In girls, a head circumference around the 10th centile combined with increased leg length and educational difficulties would raise the suspicion of XXX karyotype.

Finally all three categories have an increased incidence of delayed speech development suggesting that sex chromatin screening of patients attending speech clinics would be beneficial.

2 Abramsky L, Chaplin J. 47,XXY (Klinefelter syndrome) and 47.XXY: estimated rates of and indication for postnatal diagnosis with implications for prenatal counselling. Prenatal Diagnosis 1997;17:363–8.
13 Ratcliffe SG, Pan H, McKie M. Growth and sexual development of 47.XXY boys identified by population screening. An Esp Pediatr 1993;3(suppl 1):18–22.
17 Ratcliffe SG. The social development of boys with the chromosome constitution 47.XXY (Klinefelter's syndrome). Clin Endocrinol Metab 1982;11:703–16.