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Klinefelter's syndrome in adolescence

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SUMMARY Twelve boys with Klinefelter's syndrome (47,XXY) identified by sex chromatin screening at birth were examined at between ages 16 and 18 years, together with 12 controls matched for social class and birth order from the same newborn population. Physical examination, psychometric assessment, personality, and degree of psychosexual development were assessed without knowledge of the karyotype. Anthropometry showed increased leg length and decreased head circumference in the XXY boys. Gynaecomastia was present in 4 boys, and testicular volume was reduced in the majority but one boy had normal sized testes. On the Wechsler intelligence scale there was a significant reduction in verbal score but not in either performance or full-scale score compared with the controls. Although appreciable differences were found in growth, personality, intelligence test scores, and psychosexual development, these were of small degree.

The use of chromosome analysis in antenatal screening programmes is increasing and as a consequence obstetricians are being presented with the dilemma of how to advise parents if a sex chromosome abnormality is revealed incidentally.[1] Prospective studies of children with sex chromosome aneuploidy[2] identified in the newborn chromosome surveys which began in the late 1960s will provide answers to many of the prognostic questions about these children during the next decade, but there remains an urgent need for precise information now.

In 1964 Maclean *et al.*[3] gave the results of a sex chromatin survey carried out between 1959 and 1962 on 10 000 female and 10 725 male liveborn infants in which 20 boys with only an additional X chromosome were identified (twelve 47,XXY, three presumptive 47,XXY, and five 'mosaic 47,XXY'). As these boys represented a group with no assessment bias we felt it would be useful to review their progress in order to find out how their health and development compared with the health and development of chromosomally normal boys from the same population, and if any additional health needs had been met by the standard provision of health care. Most individuals with Klinefelter's syndrome are diagnosed in adult life at endocrine,[4–8] infertility,[9 10] or psychiatric[11] clinics, but we wished to take advantage of the neonatal diagnosis to find out if there were special problems in adolescence.

Study methods

Cases and controls. Contact had been maintained with the general practitioners (GPs) of the patients originally identified in the sex chromatin survey by way of a questionnaire sent to them each year. The names and addresses of 2 possible controls for each case were identified from the General Register of Births, taking the next 2 boys born after the index case, matching for social class of the father (Registrar General's categories) and for birth order in groupings 1–2, 3–4, and 5 or more.

After obtaining the approval of the Hospital Ethical Committee for the project, the consent of the GP was obtained; the GP was able to say how much the parents knew about the boy's chromosome abnormality, and this was borne in mind. A letter was then sent to the parents explaining the purpose of the study and offering them the opportunity for further discussion before they committed themselves to participate. All but one of the surviving chromosomally abnormal boys agreed to take part; the remaining boy had emigrated to Canada at age 2 years and could not be traced. The mean age in years at interview was 16·6 (SD 0·9) for the XXY boys, and 16·5 (SD 0·8) for the controls.

Methods

The team consisted of a paediatrician, a psychiatrist with special experience in sexual disorders, and a psychologist; only the paediatrician knew the boys' chromosome constitution, normal or otherwise.

Information about the birth and developmental history was obtained from each mother, together

with details of all illnesses and hospital admissions. A general examination of the boy was performed; this included classification of sexual development using Tanner's stages[12] and using Prader's orchidometer[13] for testicular volume. Anthropometric examination comprised weight, stature, sitting height, triceps and subscapular skinfold thickness, bi-iliac and biacromial diameters; circumference of head, upper arm, thigh, and calf; length of upper arm, lower arm, hand, calf, and foot; subischial leg length was obtained by subtracting sitting height from stature.

The psychometric part of the study was carried out on two separate occasions. At the first visit Wechsler's intelligence scale for children or Wechsler's adult intelligence scale was used followed by Bem's sex role inventory.[14] On the second occasion the high school personality questionnaire[15] forms C and D were given.

The third part of the study undertook to investigate the psychosexual development of the two groups of boys by means of a semistructured interview, with mother and son separately.

Lastly, one sample of blood was obtained for chromosome analysis and hormone assay using radioimmunoassay. The results of all tests on the XXY boys and the controls were analysed as matched pairs.

Results

Chromosome analysis. The eleven 47,XXY boys living in the UK were successfully traced and had their karyotypes confirmed. Of the 3 'presumptive XXY' boys one was confirmed to have a non-mosaic 47,XXY chromosome constitution; one infant had died on the first day of life with respiratory distress syndrome; the third boy's chromosome analysis showed a 46,XY karyotype in all cells, and a Barr-negative buccal smear.

Four of the 5 boys identified as 'mosaic 47,XXY' at birth were traced. The fifth boy had died in a drowning accident aged 5 years. Shortly before he had had a school medical examination at which no abnormality had been found and he had scored 118 on a Goodenough intelligence test. Of the 4 'mosaic XXY' boys, 3 were found to have a normal male karyotype on lymphocyte culture, at least 50 cells being analysed in each case. In the remaining boy a minor degree of mosaicism persisted. All the 12 control boys had normal male karyotypes.

The follow-up study therefore consisted essentially of 12 non-mosaic 47,XXY boys with 12 control boys matched for social class and birth order as described previously.

Demographic characteristics.

Parental age

This was calculated from the date of birth of each child and of his parents. The mean maternal age for the 12 XXY boys was 27·6 years, and for the 12 controls 27·8 years ($t = 0{\cdot}03$), while the mean paternal age for the XXY boys was 30·6 years, and for the controls 30·2 years ($t = 0{\cdot}33$). There was therefore no evidence of any parental age effect.

Early life events

The histories of the two groups of boys were compared during pregnancy, birth, and throughout early childhood and were similar for the incidence of abnormal pregnancy and delivery, neonatal resuscitation, illness, convulsions, and trauma; the only difference was in speech development. This was delayed in 4 XXY boys who had been referred for speech therapy, while only one control was recorded as having a delayed onset of speech at 3 years; thereafter he made rapid improvement in his language acquisition.

Education experience

No differences were noted between the two groups at nursery or in primary school, but in secondary school these became apparent. Among the XXY boys 8 were described as having problems, 4 with learning and 4 with behaviour—such as inattentiveness, shyness, easy crying, and excessive fighting. By comparison, only 2 control boys had learning or behavioural problems. As regards examination results, 3 XXY boys had passed school leaving tests at O (Ordinary) grade and 5 had not, compared with 6 control boys who had obtained O grade results, while 3 had not. Four XXY boys remained at school with 3 control boys.

Clinical findings

Congenital defects. One XXY boy had a foot deformity, and one had a malformed lower jaw. One control boy had multiple pigmented naevi over the trunk.

Sexual development. The most obvious difference between the two groups was in testicular size, the XXY boys characteristically having testes of 3 to 5 ml volume and of soft consistency, whereas most of the control boys had testicular volumes of 12 to 15 ml (Table 1). There were however, some exceptions. One XXY boy had testes of 10 and 12 ml volume which were of normal consistency, and he was therefore indistinguishable from the controls in

this respect. Nevertheless he had an increase in gonadotrophins indicating some testicular dysfunction. Another XXY boy had been followed up regularly at an endocrine clinic because of abnormal chromosomes, and was recorded as having gradual enlargement of his testes up to 10 and 20 ml volume on the Prader orchidometer at age 15 years, confirmed by two observers. However, when examined as part of this study at age 16½ years, testicular volumes of only 6 and 8 ml were recorded. His gonadotrophin values had been increased since he was aged 14 years. One XXY boy had an undescended testis which, when surgically placed in the scrotum, had a volume of 5 ml.

Penile and pubic hair development were less well advanced in the XXY boys than in the controls, but the difference did not reach statistical significance (Table 2).

Gynaecomastia was pronounced (Tanner's stage 3) in one XXY boy although concealed by clothing, and surgical removal was arranged shortly after our assessment. A moderate degree of gynaecomastia was present in 2 further boys and a minor degree in one. None was observed in any of the controls.

Facial and axillary hair were only slightly developed in both groups, without great differences between the two.

Anthropometric results. The mean values for each of the 17 parameters measured in the two groups of boys are given in Table 3. Paired analysis showed a significant increase in the values for subischial leg length ($P<0.02$) and calf length ($P<0.05$), and a significant reduction in the head circumference ($P<0.02$) for the XXY boys compared with the controls.

There was considerably more variability in the XXY boys than in the controls in all measures except skinfolds, this might have been related to the fact that the XXY boys were at a less advanced stage of puberty. The analysis was therefore repeated using pubertal grading (genital development) as a covariate, but excluding head circumference which is not affected in the pubertal growth spurt. With this refinement, further significant differences were obtained in stature ($P<0.001$), sitting height ($P<0.01$), upper arm, forearm, and foot length ($P<0.01$), all these measurements being larger in the XXY boys. In addition, the significance of the subischial leg length and calf length result in the XXY boys was increased ($P<0.001$). Biacromial and bi-iliac diameters conformed to normal male standards in the XXY boys, although 2 of them were at the 97th centile for the bi-iliac diameter.

Table 1 *Testicular size in XXY boys compared with controls, aged 16–18 years (number of boys in each category)*

Group	*Mean volume of both testes (ml)*			*P*
	1–5	*6–10*	*11–15*	
XXY*	8	2	1	0·004
Controls	0	2	10	

* One XXY boy refused examination.
Exact form of McNemar's test used for analysis with combination of categories to obtain 2 × 2 tables.

Table 2 *Sexual development in XXY boys compared with controls, aged 16–18 years (number of boys at each stage)*

Group	*Tanner stage*					*P*
	2	*3*	*4*	*5*	*Not known*	
Genital development						
XXY	1	3	5	2	1	NS
Controls	0	0	3	8	1	
Pubic hair						
XXY	1	4	5	1	1	NS
Controls	0	1	5	5	1	

Table 3 *Anthropometric results in XXY and control boys*

Measure	*XXY (n = 12)*		*Control (n = 12)*	
	Mean	*SD*	*Mean*	*SD*
Weight (kg)	59·0	14·1	62·2	8·9
Stature (cm)	178·4	13·5	173·6	5·5
Sitting height (cm)	90·7	8·2	91·3	4·1
Subischial leg length** (cm)	87·6	5·8	82·3	2·8
Biacromial diameter (cm)	37·7	3·5	37·3	2·5
Bi-iliac diameter (cm)	26·8	2·4	27·2	1·4
Head circumference** (cm)	55·2	2·2	56·8	1·1
Triceps skinfold	9·1	3·4	9·0	5·3
Subscapular skinfold	7·5	2·5	9·0	5·3
Upper arm length (cm)	33·3	2·9	32·8	1·3
Forearm length (cm)	25·4	2·3	24·6	0·8
Hand length (cm)	19·0	1·5	19·3	1·1
Calf length* (cm)	42·6	3·4	39·8	1·4
Foot length (cm)	26·1	1·8	25·5	1·3
Upper arm circumference (cm)	23·0	3·2	23·9	2·8
Thigh circumference (cm)	48·6	6·3	51·2	5·0
Calf circumference (cm)	32·3	3·8	34·3	2·6
Mean age (years)	16·6	0·9	16·5	0·8

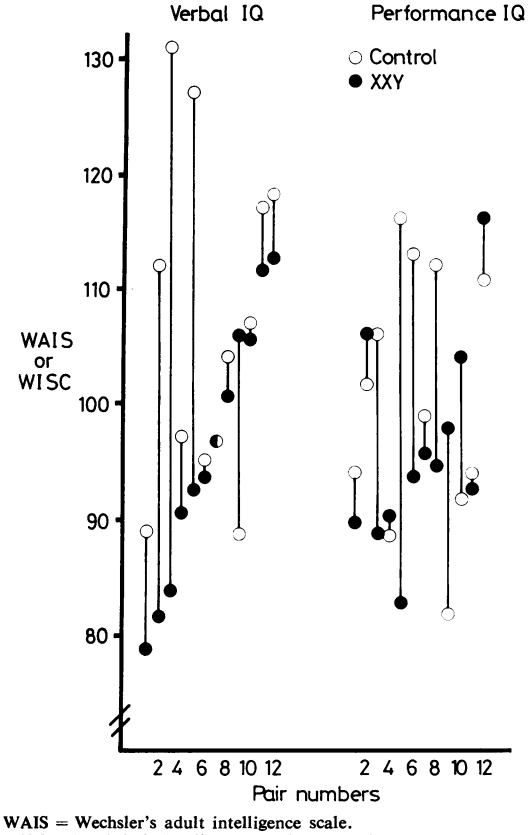
** $P < 0.02$, * $P < 0.05$.

Intelligence tests. At the appropriate ages, Wechsler's intelligence scale for children and Wechsler's adult intelligence scale were used. Differences between the results from the two tests within the control group, and within the case group were not statistically significant, so the results of both tests were analysed together as matched pairs.

Table 4 gives the mean values for the two groups, while the Figure shows the individual verbal and performance scores in pairs (for clarity, the pairs have been rank ordered for verbal IQ in the XXY).

Table 4 *Intelligence test scores in XXY and control boys*

	Verbal IQ		*Performance IQ*		*Full-scale IQ*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
XXY (n = 12)	96·5	11·4	97·0	9·1	96·3	10·3
Control (n = 12)	106·9	14·2	101·7	10·7	104·7	12·3
Two-tailed *t* test	P < 0·02		NS		NS	



WAIS = Wechsler's adult intelligence scale.
WISC = Wechsler's intelligence scale for children.

Figure *Verbal and performance intelligence scores in XXY boys and controls.*

Paired analysis with the 2-tailed *t* test showed a significant lowering of verbal score (P<0·02), but only a suggestion that the full-scale score might be reduced (P<0·1) in the XXY boys. There was no significant difference in performance scores between the XXY boys and the controls.

Although the XXY boys scored lower than the controls in each subscale, the difference was significant only for comprehension.

No boy scored in the subnormal range.

Personality tests and psychosocial development. The detailed results of these tests will be published elsewhere,[27] but the main findings are summarised here.

On the high school personality questionnaire the most significant difference (P<0·001) was in the 'mental capacity and ability to abstract' subscale, where the XXY boys performed less well. In addition, the XXY boys rated themselves as 'more tender minded, apprehensive, and insecure' than the controls (P<0·02), but not as more aggressive. They reported appreciably more problems with peer group relationships and less sexual interest in girls with only one XXY boy meeting a girl regularly compared with 5 controls. As regards masturbatory activity the age of onset was almost a year later in the XXY boys compared with the controls (14·3 compared with 13·4 years) but the number masturbating in each group and the frequency of masturbation were not significantly different between the two groups.

On the Bem sex role inventory small differences were again apparent. In this test each subject rates himself on a scale for a number of personality characteristics of which one-third are popularly linked with masculinity, one-third with femininity, and the remaining one-third are neutral but socially desirable. The masculinity score of the XXY boys was significantly lower than that of the control boys, while the feminity and neutral scores were reduced to an extent which did not quite reach significance. As the attributes are generally socially desirable a universal lowering could have reflected a reduced self-esteem.

An analysis of the extent to which the boys' interests and activities were typically masculine or feminine did not show any differences between the groups either during childhood or adolescence.

No boy in either group described himself as having homosexual interests.

Hormone analysis. A single blood sample was taken between 1000 and 1200 hours. The mean values for testosterone, luteinising hormone (LH), and follicle-stimulating hormone (FSH) are shown in Table 5. The mean testosterone level was significantly lower in the XXY boys (P<0·01).

Corresponding increase in gonadotrophins was present, the differences being significant (LH P<0·01 and FSH P<0·002). The XXY boys who were at the earlier stages of puberty had LH levels within the normal range, but the FSH levels were all above normal.

Spermatozoa in urine. On the day of the clinic visit the first specimen of urine passed that morning was examined for the presence of spermatozoa. These

Table 5 *Hormone levels in XXY and control boys*

	Testosterone (nmol/l)		*Luteinising hormone (IU/l)*		*Follicle-stimulating hormone (I U/l)*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
XXY (n = 11)*	14·06	5·17	19·64	13·10	37·56	22·40
Controls (n = 12)	21·60	7·74	5·28	2·56	4·57	4·11
Two-tailed *t* test	$P < 0·01$		$P < 0·01$		$P < 0·002$	

*One boy excluded because of insertion of a testosterone implant 3 months previously.
Conversion: SI to traditional units—testosterone: 1 nmol/l ≈ 0·288 µg/l.

were identified in samples from 3 control boys but from none of the XXY boys.

Discussion

In children and adolescents Klinefelter's syndrome is rarely diagnosed, the reports of it being mainly of patients identified by chromosome or sex chromatin screening at child psychiatric clinics.[16 17]

Annell and Gustavson[16] identified 8 XXY boys and 2 mosaic XXY boys out of 620 children attending the department of child and youth psychiatry in Uppsala, an incidence of 1·3%, about 10 times that found in the newborn.[2] The children were seen between ages 3 and 12 years and presented with problems related to difficult peer relationships, slow learning at school, and aggressive behaviour. All had testes that were smaller than normal, and verbal IQ scores which were lower than their performance scores. The authors reported that relief of the children's problems was achieved by parental counselling, school adjustments, and remedial teaching, and the use of oral methyl testosterone for brief periods in 2 boys had resulted in behavioural improvement.

Funderburk and Ferjo[17] described 11 XXY boys who were identified in a cytogenetic survey of consecutive child psychiatric patients reported by Crandall *et al.*[18] Presenting complaints were of school underachievement in 9 boys, withdrawal and apathy in 8, impulsive aggressive behaviour in 6, and faecal retention and soiling in 5. There was a high incidence of speech and language problems but this was not reflected in their mean verbal and performance IQ scores of 93·6 and 93·0 respectively. Gynaecomastia and skeletal abnormalities were present in 3 of the 4 patients over age 17 years.

Of the 11 cases of Klinefelter's syndrome, aged between 8 and 12 years, which Nielsen *et al.*[19] described from a child psychiatric clinic, only 2 had been diagnosed as having this condition in childhood. These 11 boys had a mean IQ score of 95·1 ± 8·4 and had had behavioural disturbances for several years. They were described as being immature, having difficulties in personal relationships and with learning at school, while 7 had been taking part in petty larceny. Nine of the 11 cases were diagnosed as having Klinefelter's syndrome when presenting with other symptoms in early adult life.

Caldwell and Smith[20] reported 3 XXY boys, 2 of whom presented with learning difficulties and fatigue, while the third complained of his small genitalia. These authors advocated the use of testosterone supplementation in all XXY boys starting at age 11 to 12 years with the aim of preventing gynaecomastia and improving secondary sexual development, and the related sexual problems. They also stated 'because of sampling bias the incidence of significant mental subnormality among boys with the XXY syndrome is uncertain'.

The effect of sampling bias is stressed when these reports are compared with the current study. None of the 12 boys described here had been referred to a psychiatric clinic, although one control boy had been referred by the children's panel for psychiatric help. Although the mothers and boys described difficulties in school and in peer relationships, these were not of such severity that help had been sought outside the family.

Our growth studies showed the increased leg length found in adult XXY patients, and confirmed the findings of the smaller head circumference of XXY boys from the follow-up of our newborn chromosome survey.[21] We were unable to define accurately the time of onset of puberty in these boys as we did not see them over a prolonged period of time, but at the time of assessment it was clear that progression of pubertal changes had been slower in the XXY boys than in the controls. In the Zurich study[22] puberty was reported to start slightly later in the XXY boys but the difference was not significant at the 5% level. The normal size of the testes in 2 boys shows our lack of knowledge of the development of the testicular lesion in Klinefelter's syndrome and should introduce a note of caution about making prognostic statements on later fertility.

In their endocrinological study of the XXY young men identified by population screening of tall army recruits[23] Schiavi *et al.*[24] did not give the precise number with gynaecomastia but implied that fewer than half of the 14 XXY men they studied were affected. The incidence of gynaecomastia found in the current study is likely to be an underestimate and will increase during the next 10 years of the boys' lives. None of these boys had sought treatment for the gynaecomastia despite the social embarrassment

it had caused them. Furthermore, the one undescended testicle had escaped detection at the routine school medical examination performed on 13-year-old pupils.

As regards intelligence, reports in adults have stressed the lower IQ in patients with Klinefelter's syndrome. Ferguson Smith[25] estimated that subnormal intelligence was present in half of them, whereas Becker[7] stated that one-quarter of his 104 patients held posts of considerable responsibility—such as physicians, ministers, accountants, engineers, and architects. Clearly the source of the clinical population has an effect on the distribution of intelligence found, and the true incidence of subnormality can only be found by excluding selection bias.

Witkin *et al.*[23] studied 16 XXY men identified by chromosome screening of tall (>184 cm) army recruits and showed a significant reduction in the scores obtained by XXY men using a Danish group test, the Børge Priens Prøver. This test covers only a limited number of cognitive dimensions and cannot easily be compared with the more widely used tests such as Wechsler's intelligence scale. Bearing these limitations in mind the 16 XXY men obtained scores of 28·4 (SD 14·1), compared with a score of 43·7 (SD 11·4) in the tall XY men. It is of interest to compare these intelligence test results with the preliminary findings of the newborn longitudinal studies already mentioned.

Stewart *et al.*[26] identified 43 XXY boys in a study of sex chromatin abnormalities using amnion cells, and 29 of these children are taking part in a longitudinal study. Siblings were used as controls and were considerably older than the cases. Assessment using McCarthy's scales of children's abilities at age 7·15 years in the cases and at age 12·15 years (SD 7·32) in the controls showed no significant difference in the general cognitive index (92·25 (SD 14·38) for XXY, compared with 98·5 (SD 13·08) for the controls); however there was significant reduction in the memory score ($P < 0·02$) and the motor score ($P < 0·05$) in the XXY boys. The authors admit that age matching fell short of ideal, and it is clear that with follow-up results for only 67% the results may not represent the true range of IQ scores for the whole group.

Our current longitudinal study of children with chromosome aneuploidy started in 1967 and identified 23 XXY infants of whom one died shortly after birth at 28 weeks' gestation. Nineteen of these children are the subjects of the longitudinal study and up to the present time results are available on 12 using the Stanford Binet test (Terman-Merrill norms) at age 4 years. The XXY boys obtained a mean score of 100·7 (SD 15·97) compared with 116·97 (SD 15·05) from 88 social class matched controls from the same population. The high IQ from the control population should not be unexpected if the social class structure is examined (that is 40% in social classes I and II).

Eight of these children have reached age 7 years and on Wechsler's intelligence scale for children have a mean full-scale score of 102·3, verbal 100·4, performance 103·4 (full-scale range 70–131). These results are in good general agreement with those from the adolescent group, and indicate that if assessment bias is removed the reduction in intelligence is slight. The findings in the adolescent boys confirm those of other authors[4 8 16] in showing a poorer verbal than performance ability and demonstrate the persistence of the language deficit that can be detected as early as age 2 years.[28] It should be stressed that performance IQ was not reduced and that no boy was found to be in the subnormal range.

On the basis of those studies, which can be regarded as unbiased, we can conclude that the reduction of intelligence test scores is of minor degree, although statistically significant, and therefore there would appear to be little justification for abortion of an XXY fetus on the grounds of the risk of mental subnormality. In the XXY boy one may expect a higher than average incidence of problems with speech development, with learning at school, and of social adjustment in adolescence. In view of the fact that a number of the problems described here are amenable to treatment it would be of benefit for all XXY boys to be under regular medical supervision during puberty and should the therapeutic regimen recommended by Caldwell and Smith[20] gain general acceptance it would be necessary to identify such boys during mid-childhood. At present this could only economically be achieved by population screening for sex chromatin abnormalities rather than by routine chromosome analysis.

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