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Follow-up 20 years later of 34 Klinefelter males with karyotype 47,XXY and 16 hypogonadal males with karyotype 46,XY

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Summary.

A 20-year follow-up study of 50 hypogonadal males has been made. Of these 34 had Klinefelter's syndrome with the karyotype 47,XXY and 16 had the karyotype 46,XY. These males have been examined at mean ages of 27 and 37 and in the present study at a mean age of 47. At the first examination the following conditions were found in the Klinefelter males to a significantly higher degree than in the hypogonadal males with 46,XY: immaturity, below average school performance, few or no friends, previous mental illness, little energy and initiative, few or no spare time interests, occupation as an unskilled labourer. Psychological testing showed a full scale IQ of 103 in the Klinefelter males and 115 in the hypogonadal males. The follow-up studies have shown that in spite of these findings the Klinefelter males have managed far better than could have been expected at the time of the first investigation. The improvement in a number of conditions such as mental health, working capacity, social adjustment, relations with other people, and activity level was considerable between the ages of 27 and 37. The present examination shows a further improvement at the age of 47 with the only significant difference between the Klinefelter males and the hypogonadal males with 46,XY being a higher frequency of single Klinefelter males. The present examination also showed that there was no significant difference between the two groups in occupation, working capacity, social adjustment, mental and physical disorders or criminality. The rest of the examination at the mean age of 27 would probably have been considerably more favourable for the Klinefelter males if diagnosis had been made in childhood, and information, counselling, support and hormone treatment had been given from an early age. The fact that the great majority of the Klinefelter males have managed quite well in spite of this and that no remarkable differences were found between them and

a control group is of great importance for genetic counsellers, especially for prenatal counsellers. Up until now, in 75% of cases in which sex chromosome abnormalities, including Klinefelter's syndrome, have been diagnosed prenatally in Denmark abortion has been induced. We believe this is mainly due to insufficient information about the many positive aspects of the development of individuals with sex chromosome abnormalities.

Introduction

During the years 1965-1966, 50 severely hypogonadal males were examined by two psychiatrists and a psychologist (Nielsen et al. 1969; Theilgaard et al. 1971). They had previously been studied in 1965 (Frøland 1969), and a follow-up study was made 10 years later in 1975 (Nielsen et al. 1980).

The present study is the second of a series of follow-up investigations of the 50 probands scheduled for 10-year intervals until they have reached the mean age of 77, 50 years after the original study when their mean age was 27. These follow-up studies have been planned partly in order to learn more about the differences between Klinefelter males with karyotype 47,XXY and hypogonadal males with a normal karyotype 46,XY, and partly in order to give advice, support and hormone treatment to those in need of it. This follow-up study is comparable to those carried out on unselected children with sex chromosome abnormalities discovered at birth Nielsen and Sillesen 1976; Nielsen et al. 1979, 1982; Robinson et al. 1982; Ratcliffe et al. 1982; Stewart et al. 1982; WaIzer et al.1982; Leonard et al. 1982; Higurashi et al. 1982).

Longitudinal studies are needed for all groups with sex chromosome abnormalities in order to learn more about the development, behaviour, risk of mental and physical disorders and the possible value of information, advice, support and treatment. Such data are needed for those giving information to parents of boys with Klinefelter's syndrome or to Klinefelter males and for prenatal genetic counsellers to give sufficiently balanced information to parents of a foetus with Klinefelter's syndrome.

Materials and methods

Materials and some results from the first examination in 1965-1966

The 34 patients with karyotype 47,XXY group A) were identified by sex chromatin examination of all hypogonadal males attending the Male Hypogonadism Study Section at the Medical Out-patients' Clinic, Copenhagen University Hospital, from January 1953 to April 1965. All such males received X-chromatin examination, and chromosome analysis was carried out on those with X-chromatin positive cells.

The control group with the chromosome constitution 46,XY (group B) was detected at the same clinic among the hypogonadal chromatin negative patients on whom a testicular biopsy had been made. All such patients, who had a greatly reduced sperm count, were included. Patients in whom no sperm count was available were included if the testicular picture showed severe impairment of spermatogenesis.

At the time of the first examination the mean ageof the 34 males in group A was 27.2 +/- 9.6 and the mean age of the 16 mates in group 13 was 27.6 +/- 6.0.

Table 1. *Distribution by karyotype and psychiatric raw scores with significant differences between patients in group A and patients in group B and IQ at the first examination in 1965-1966*

Anamnestic information and psychopathological symptoms	**Group A 47,XXY (n=34)**		**Group B 46,XY (n=16)**		**P (Fisher)**
	Total	%	Total	%	
Immature	27	79	3	19	0.0001
School performance below average	20	59	1	6	0.0007
Few or no friends	14	41	0	0	0.0002
Previously mentally ill	14	41	0	0	0.0002
Little energy and initiative	12	35	0	0	0.0090
Insecure	27	79	6	38	0.0101
Few or no sparetime interests	18	53	2	13	0.0125
Word-blind	10	29	0	0	0.0255
Poor relations with parents or siblings	10	29	0	0	0.0255
Unskilled labourer	13	38	1	6	0.0346
	(*n*=25)		(*n*=14)		
Weak sexual libido (age 20+)	12	48	0	0	0.0027

Never had sexual intercourse (age 20+)	11	44	0	0	0.0053

Psychological test scores	**Mean +/-SD**	**Mean +/- SD**	**Student *t*-test**
Full-scale IQ	102,8 +/- 11.2	115,3 +/- 12.1	0,001
Verbal IQ	101.9 +/- 13.4	117.6 +/- 12.8	0.001
Performance IQ	103.4 +/- 9.0	110.3 +/-11.6	0.05

The psychiatric - psychological examination was conducted by investigators who were unaware of the group to which the subjects belonged. The mental state of group B was substantially normal compared with various deviations in the mental development of.the majority of males in group A (Table 1). There was no difference between the occupational status of the fathers and brothers of the two groups, but, as shown in Table 1, there was a significantly higher frequency of unskilled labourers in group A (*P* =0.03, Fisher's exact probability).

Methods in the present study

A letter was written to each of the 50 probands asking them whether they would-participate in a follow-up examination by telephone interview with the purpose of discussing their health and life conditions during the decade since the last follow-up examination. It turned out that 5 of the Klinefelter males (16%) and 3 of the 16 males with 46,XY (19%) did not wish to participate. The majority answered the first letter, but in a number of cases a second and in a few cases a third letter was sent before any answer was received.

The~telephone interview took betweeti 45 and 60 min, and the probands were asked about the following items over the last 10 years:

1. Occupational conditions - working periods, type of work, work adjustment, working capacity and periods of unemployment.

2. Conditions of living - house, apartment etc. Changes of any kind during the last 10 years were noted.

3. Health conditions and disorders since last examination, both physical and mental. Medical treatment and other kinds of treatment.

4. Sexual conditions, especially changes during the last 10 years.

5. Marital or cohabital conditions during the last 10 years.

6. Hormone treatment during the last 10 years.

7. Attitude towards the investigation.

The majority of the probands were positive and co-operative towards the follow-up investigation and stated that they would welcome further contact. Several said that they considered such a follow-up a valuable service which gave them the opportunity to ask delicate questions about their hormone disorder, the possibilities of becoming the biological father of a child, adoption, donor examination, sexual libido, potency and hormone treatment as well as a number of other physical and psychological problems. The information given by the probands concerning physical and mental disorders was supported by information from hospital records and general practitioners.

The five Klinefelter males who did not want to participate in the study did not deviate from the responders concerning occupation, education and social level (their occupations were architect, house painter, office clerk, mechanic, factory worker and publicity artist). Nor did the three 46,XY males deviate from the rest concerning occupation, educational and social level. One was an engineer, one a graduate engineer and one a plumber. There was no indication that these eight males had any increased frequency of mental illness or deviated from the rest of the group in any special way, except for not wanting to keep in contact with us.

The follow-up study would have gained in objectivity if it had been conducted by a personal interview, the interviewer being without previous knowledge of the patient. However, an investigation of this type would almost certainly have been unsuccessful because several probands would have refused to make contact with an unknown investigator.

Results and discussion

Occupation; and employment

At the first examination at a mean age of 27 and at the follow-up examination 10 years later there was a significantly higher frequency of unskilled labourers among the Klinefelter males; however, this difference has disappeared at the mean age of 47 (Table 2). The great majority of the Klinefelter males have a job, and unemployment is not more frequent among Klinefelter males than among the controls. Nor was there any significant difference between the Klinelelter males and the hypogonadal males concerning changes in job responsibility (Table 3) These findings are supported by a lack of any

significant difference between the two groups in social adjustment (Table 4): only 4 of the 29 Klinefelter males were poorly socially adjusted.

It is remarkable that Klinefelter males studied have by now reached the same occupational and employment level as the controls in spite of the significantly higher frequency of psychological problems and lower educational and social level found when they were first examined at the mean age of 27. This leads us to believe that the great majority of.Klinefelter males, at least in Denmark, live a normal active working life very much like other males of their age. The finding of an improvement in their social and occupational level from the first examination 20 years ago to the present examination shows the importance of longitudinal studies, preferably on unselected groups.

Table 2. *Occupational status and unemployment.*
There was no significant difference between group A and group B

Occupational status and unemployment	Group A 47,XXY (*n*=29)		Group B 46,XY (n=13)	
	Total	%	Total	%
Higher education	7	24	5	38
Skilled labourer	12	41	6	46
Unskilled labourer	10	34	2	15
Unemployed*	4	14	1	8

Table 3. *Change in job responsibility during the last 10 years.*
There was no significant difference between group A and group B

Job responsibility	Group A 47,XXY (*n*=29)		Group B 46,XY (*n*=13)	
	Total	%	Total	%
Increased	12	41	7	54
Decreased	4	14	1	8

No change	13	45	5	38

Table 4. *Social Adjustment.*
There was no significant difference between group A and group B.

Social Adjustment	Group A 47,XXY (n=29)		Group B 46, XY (n=13)	
	Total	%	Total	%
Well	19	66	12	92
Fairly well	6	21	1	8
Poorly	4	14	-	-

Marital state and adoption

Table 5 shows that 38% of the Klinefelter males were single at the mean age of 47 compared with none of the hypogonadal males with 46,XY (P <0.05); however, 59% of the Klinefelter males were married compared with 92% of the control group. The difference was not significant nor was the divorce rate significantly higher among Klinefelter males. Adoption was similar in both groups and rather frequent. Ten of the 17 married Klinefelter males had adopted a child and in all cases with quite satisfactory results.

Table 5. *Marital state and adoption*

Marital State	Group A 47,XXY (n=29)		Group B 46,XY (n=13)		Fisher´s exact test
	Total	%	Total	%	
Married [a]	17	59	12	52	P=0.0582
Single	11	38	-	-	P=0.0161
Never married	6	21	1[b]	12	P=0.5735
Divorced during the last 10 years	5	17	1	8	P=0.7697
Adoption by those married	10	59	11	92	P=0.1200

a. Includes those who have lived together with a girl friend for more than 3 years

b. Has lived with his girl friend for 2 years

Table 6. *Criminality since the last examination 10 years ago. There was no significant difference between group A and group B*

Criminality	Group A 47,XXY (*n*=29)		Group B 47,XY (*n*=13)	
	Total	%	Total	%
Violation of penal code	4	14	1	8
All types of criminal behaviour	6	21	2	16

The higher frequency of single males in this group is no doubt largely due to the fact that none of these males were diagnosed and treated with testosterone at a reasonably early age, that is from the age of 11-12. Most of them were not treated: only 4 of the 36 Klinefelter males were treated at the time of the first examination at a mean age of 27. This shows the great importance of early diagnosis of males with Klinefelter's syndrome (Nielsen and Sørensen 1984).

Hormone Treatment

Only 9 of the 29 Klinefelter males were treated with testosterone compared with none of the 13 hypogonadal males with 46,XY. The effect of the hormone treatment was considered favourable in all nine cases.

Testosterone treatment in adequate doses from the time of increase in follicular stimulating hormone, around the age of 11, helped to prevent the development of deviations in behaviour and learning abilties at school. Hormone treatment also stimulates and increases the level of activity and general well-being and may prevent osteoporosis, back ache and the excessive tiredness often found in males with Klinefelter's syndrome (Annell et al. 1970; Caldwell and Smith 1972; Fromantin et al. 1974; Johnson 1975; Sørensen et al. 1981; Nielsen and Sørensen 1984).

Criminality

There was no significant difference between the two groups concerning criminal behaviour during the last 10 years (Table 6), nor was there any significant difference in criminal behaviour at the last examination 10 years ago. However, at the first examination at the mean age of27, the frequency of criminality was significantly higher in the Klinefelter group (38%) compared with the hypogonadal group (6%) (*P*(Fisher) =0.0346).

Table 7. *Disorders during the last 10 years.*
There was no significant difference between group A and group B

Physical and mental disorders	Group A 47,XXY (*n*=29)		Group B 46,XY (*n*=13)	
	Total	%	Total	%
Cardiovascular disorders[a]	8	27	2	15
Vascular disorders of legs	5	17	1	8
Severe backache	4	14	-	-
Mental illness[b]	5	17	1	8

a Includes vascular disorders of the legs

b All were admitted to a psychiatric hospital

The decrease in the frequency of criminal behaviour over the years parallels the improvement in a number of conditions including social adjustment, work capacity and adjustment as well as general well-being.

Disorders

Physical illness. There was no significantly increased frequency of physical disorders in Klinefelter males (Table 7). However, the proportion of the Klinefelter males with vascular disorders of the lower extremities is high, at 17%, and ulcus cruris has been reported to occur 3-30 times more frequently in Klinefelter males than expected in the general population (Breit 1984). The increased frequency of vascular disorders may again be due to the fact that few in our group were treated with testosterone from an early age or at all.

The low concentration of plasma testosterone affects the relationship between oxidised and reduced haemoglobin, especially in areas with large veins, such as the legs. An increased concentration of reduced haemoglobin may lead to oedema and be one of the causes for the comparatively high frequency of oedema, ulcus cruris and vascular disorders in the legs in general in Klinefelter males. Women with.three X chromosomes have an increased concentration of coagulation factor 8 (Mantle et al. 1971), but changes in factor 8 concentration have not been investigated in Klinefelter-males.

An example of a Klinefelter male with vascular disorders of the legs is provided by a 38-year-old male with karyotype 47,XXY who has suffered from varicose veins and a tendency to oedema on his legs since the age of 20. At the age of 22 he was operated on for varicose veins in both legs. Dodd's operation was later performed on the left leg. He has had a skin transplant several times in the local hospital and in the University Hospital of Copenhagen, each time with unsaisfactory results. Artheriography has shown occlusions of the poplitea artheria on both sides, and there is also decreased pressure on measurement of the pressure of perfusion. On the outer side of the right foot there is a 3 cm ulcer with outstamped edges and on the inner side of the right foot there is a further 3x3x2 cm ulcer. The diagnosis is thrombangitis obliterans Buerger with ulcus chronica cutis.

Mental illness. There was no significantly increased frequency of Klinefelter males admitted to psychiatric hospitals or males with mental illness, and the frequency of 17% admitted over a 10-year period is not exceptionally high. All 5 Klinefelter males with hospital admission for rnental illness had a diagnosis of personality disorders; 3 also showed alcohol abuse, and 2 of these also shared drug abuse. None of the 5 Klinefelter males suffered from psychoses. The 46,XY males with mental illness had a diagnosis of sexual neurosis. None of the 29 Klinefelter males was in a psychiatric hospital at the time of the examination, and none was considered to be in need of psychiatric treatment. This is in contrast to the findings at the first examination at a mean age of 27; at that age we found that 41% of the Klinefelter males had had a mental illness or suffered from mental illness at the time of the examination compared with none of the controls ($P<0.0021$).

The treatment of Klinefelter males with psychoses or other types of mental illness should follow the guidelines given by Nielsen et al. (1980).

The finding of a significantly higher frequency of psychological problems and mental illness up to the mean age of 27 is probably due to the late diagnosis of Klinefelter's syndrome in most of these males. The increased frequency of mental illness might have been reduced if the diagnosis had been made early in childhood and if information, counselling and advice had been given to the parents concerning the development of Klinefelter's syndrome, and the need for specially stimulating, stable and good childhood conditions for these boys (Nielsen and Sørensen 1984). If the diagnosis had been made early, and

testosterone treatment given from the age of 11-12, then the development of certain types of mental illness and psychological problems in the young adult Klinefelter males would probably have been prevented.

Measurement of the testes in all school boys at the age of puberty and chromosome examination of those with testes below 2 ml would lead to the diagnosis of all cases of Klinefelter's syndrome. Such a screening method would be an easy and natural part of the prophylactic examination procedure made by school physicians in most countries.

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