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Mortality ratios and life expectancy in X chromatin positive males

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SUMMARY In a prospective study of 466 X chromatin positive males an increase in mortality of about 50% has been observed. The increase is associated with a loss of about five years in life span. There is no convincing evidence that the increase is concentrated at any particular age group but this possibility could not be excluded. No effect of mode of ascertainment could be demonstrated. From this study we conclude that it is likely that the mortality experienced by chromatin positive males in general is at least 115% of that experienced by normal men and could be more than 200%.

One or two males in every thousand of the male population have a female nuclear X chromatin (chromatin positive) pattern.[1] They have an abnormality of the sex chromosome constitution,[2 3] the essential feature of which is the presence of at least one additional X chromosome, the usual complete chromosome complement being 47,XXY.[4] Affected men usually present in adult life because of infertility and hypergonadotrophic hypogonadism. A proportion also have gynaecomastia (Klinefelter's syndrome).[5] There is an increased risk of mental retardation and about one in every hundred institutionalised high grade retardates are chromatin positive.[6] The chromatin positive status can be recognised from early embryonic life but the condition is only rarely diagnosed clinically in infancy and childhood. There is, however, evidence of an increased infant mortality, and in a study of 296 male infant deaths in Moscow, Bochkov[7] found 10 chromatin positive males, while in studies of liveborn males in the UK, USA, and Canada,[8–10] six infant deaths, mostly in the immediate postnatal period, have been reported in a total of 111 babies with a 47,XXY chromosome complement. The prevailing national infant mortality rates at the time of these studies were in the region of 20 per thousand. There is no published information on mortality in chromatin positive males after the first year of life.

In 1959 Professor W M Court-Brown set up in Edinburgh a register of subjects with chromosome abnormalities. One of the main objects was a long term prospective mortality study. Since then patients have been notified to this register from all parts of the UK, particularly from Scotland and the north of England. Deaths among chromatin positive males included in this study have previously been reported,[11] and in this paper we describe the mortality ratios and life expectancy (after the first year of life).

Methods

Subjects of this report are chromatin positive males registered between 1959 and 1983. We have divided them into four categories by mode of ascertainment: (1) patients referred because of hypogonadism, gynaecomastia, and subfertility to endocrinology and subfertility clinics, and those identified in cytogenetic surveys of sections of a general (non-institutionalised) population; (2) patients identified in psychiatric hospitals in the course of routine clinical and cytogenetic assessments or in specially designed surveys of such hospitals; (3) patients found incidentally to have features of Klinefelter's syndrome (KS) and chromatin positive nuclear sex during the course of clinical assessment in general hospital wards and clinics. This group has been subdivided on the basis of whether the illness which had led to the hospital attendance was likely to cause a reduction in life span (group 3a) or not [3b] (table 1).

Since 1965 each registered patient has been followed up by annual questionnaire to the patient's medical attendant. Reports of death have been confirmed with the Registrars General for England and Wales and for Scotland.

For each individual the years at risk have been calculated from date of registration to date of exit

Table 1 *Chromosome constitution and ascertainment category of chromatin positive males*

Chromosome constitution	Ascertainment category*			
	I	*II*	*IIIa*	*IIIb*
47,XXY	232	97	49	23
46,XX	12	2	3	0
48,XXYY	2	18	0	0
48,XXXY and 49,XXXXY	1	10	0	0
46,XY/47,XXY mosaics	12	7	8	1
Other mosaics	2	19	5	0
Not analysed	24	4	1	0
Totals	285	157	66	24

* I Ascertained because of hypogonadism, gynaecomastia, and subfertility at endocrinology and subfertility clinics, or identified in cytogenetic surveys of sections of a general (non-institutionalised) population.
II Ascertained in psychiatric hospitals in the course of routine clinical and cytogenetic assessments or in specially designed surveys.
III Found incidentally to have features of Klinefelter's syndrome when referred to general medical wards and clinics because of diseases
(a) likely to cause a reduction in life span
(b) not likely to cause a reduction in life span.

from the study. In the tables these are shown in groups of five calendar years and 10 year age groups (table 2). The years at risk matrix is also subdivided with respect to the geographical area of ascertainment (England and Wales *versus* Scotland). A cumulative three dimensional matrix for each ascertainment group is then calculated by addition of the individual matrices. The expected deaths for each group are calculated by multiplying the elements of the cumulative matrix for each calendar year, five year age group, and geographical area by the relevant standard mortality rates for England and Wales and for Scotland. The mortality rates for 1983 are not yet available so we have assumed rates identical with those for 1982. The expected deaths are presented, along with the observed deaths, by age group and as an all ages figure. In comparing these figures and in the calculation of confidence limits on the standardised mortality ratio, we utilised the equations presented by Liddell.[12]

The methods of inter-ascertainment group comparison and of construction of the life tables are described in the appendix. All calculations were performed by a computer program written by one of us (JC) in the "C" programming language.[15]

Table 2 *Age at ascertainment of chromatin positive males*

Category of ascertainment	Age at ascertainment (yr)							
	1–14	*15–24*	*25–34*	*35–44*	*45–54*	*55–64*	*65–74*	*75+*
I	64	69	94	39	11	3	5	0
II	12	41	24	26	27	18	5	4
IIIa	7	4	3	11	9	17	11	4
IIIb	2	6	3	4	4	4	1	0

Results

A total of 532 chromatin positive males have been followed up since registration. An additional 29 were registered but excluded from this study. Of these, six were excluded because of coexistent trisomy 21, 21 because insufficient information for follow up was provided at the time of registration, one because permission for follow up was refused, and one because of aberrant clinical findings.

In ascertainment group I, 285 individuals have been observed for a total of 4323 man years. The breakdown of this figure, by age group and calendar year, is shown in table 3. In this group 28 deaths were observed, and the expected deaths were 19·8. This is an increase in mortality of 41% which just fails to achieve significance on a two tailed test ($0{\cdot}05<p<0{\cdot}10$). The 95% confidence limits for the relative mortality of this group (with respect to normal) are 0·94–2·04. In this group 13 individuals were lost to follow up. If all of these had been observed to date they would have contributed a further 0·3 deaths to those expected.

In group II, 157 individuals have been observed for 2041 man years (table 4). Because this group was older at ascertainment than group I, the expected number of deaths is higher (27·6) despite the fewer years of follow up. The observed deaths are significantly raised at 44 ($p<0{\cdot}01$), an increase in mortality of 59%, the 95% confidence limits for relative mortality being 1·15 to 2·14. Only one of this group was lost to follow up.

The 66 individuals in group IIIa experienced 35 deaths, far in excess of the expected figure of 9·7. In view of the totally biased mode of ascertainment (with respect to mortality) no further analysis has been undertaken.

Of the individuals ascertained because of physical illness, we felt that only 24 were at no risk of increased mortality (group IIIb). The expected number of deaths in this subgroup was 2·9 and the actual deaths 6 (table 5). The small sample prevents further useful analysis.

Patients in groups I and IIIb were ascertained because of non life threatening conditions. It is likely that they were drawn from the same pool of KS subjects in the population. We feel it is reasonable to combine the data from these groups to assess the risk of mortality to KS patients in the general population. This produces an expected number of 22·7 and actual number of 34 deaths. This increase is significant ($p<0{\cdot}05$), and the 95% confidence limits for the relative mortality are 1·03–2·09. We were unable to demonstrate any difference between this combined group and group II in terms of mortality ($\chi^2 = 0{\cdot}24$), but as the modes of ascertainment are so disparate, it

Table 3 *Man years at risk and mortality: chromatin positive males in category I*

	Age (years)								
Calendar year	*1–14*	*15–24*	*25–34*	*35–44*	*45–54*	*55–64*	*65–74*	*75–84*	*>85*
1960–4	35·2	70·8	115·7	56·1	14·0	6·0	0·0	0·0	0·0
1965–9	109·9	133·6	187·5	208·3	53·9	19·1	4·6	0·0	0·0
1970–4	135·1	140·5	260·5	279·1	140·6	25·9	12·0	0·4	0·0
1975–9	118·7	109·6	299·1	276·2	225·6	53·0	21·3	7·8	0·0
1980–3	115·5	122·6	236·6	320·2	262·3	116·0	18·9	10·8	0·4
All	514·3	577·2	1099·5	1139·9	696·4	220·0	56·8	19·0	0·4
Deaths									
Observed	1	0	2	7	6	6	5	1	0
Expected	0·3	0·6	1·3	3·0	5·5	4·5	2·9	1·8	0·0

Total observed deaths: 28.
Total expected deaths: 19·8.

Table 4 *Man years at risk and mortality: chromatin positive males in category II*

	Age (years)								
Calendar year	*1–14*	*15–24*	*25–34*	*35–44*	*45–54*	*55–64*	*65–74*	*75–84*	*>85*
1960–4	14·8	30·7	27·2	25·0	19·4	18·3	6·1	8·1	0·0
1965–9	17·3	84·6	45·1	58·1	65·7	51·0	26·6	10·2	0·5
1970–4	5·3	72·7	102·0	66·2	102·8	66·5	44·3	9·5	0·0
1975–9	0·2	74·6	178·4	94·6	96·3	88·2	50·0	14·3	4·8
1980–3	0·0	28·4	159·7	156·5	85·0	90·2	42·9	15·0	1·1
All	37·5	291·0	512·4	400·4	369·1	314·2	169·9	57·0	6·3
Deaths									
Observed	0	0	2	1	5	17	10	7	2
Expected	0·0	0·3	0·5	0·8	2·6	6·2	8·6	7·0	1·6

Total observed deaths: 44.
Total expected deaths: 27·6.

Table 5 *Man years at risk and mortality: chromatin positive males in category IIIb*

	Age (years)								
Calendar year	*1–14*	*15–24*	*25–34*	*35–44*	*45–54*	*55–64*	*65–74*	*75–84*	*>85*
1960–4	3·3	3·5	5·2	0·0	7·8	0·0	1·3	0·0	0·0
1965–9	10·0	7·1	7·9	8·5	7·6	8·9	0·0	0·0	0·0
1970–4	6·2	12·6	15·8	17·0	0·8	19·8	2·1	0·0	0·0
1975–9	1·8	11·1	22·8	13·9	15·4	9·3	11·8	0·0	0·0
1980–3	0·0	8·4	18·8	18·7	22·9	11·8	5·1	0·0	0·0
All	21·3	42·8	70·4	58·2	54·4	49·8	20·4	0·0	0·0
Deaths									
Observed	0	0	0	0	1	0	50	0	0
Expected	0·0	0·0	0·1	0·2	0·4	1·1	1·1	0·0	0·0

Total observed deaths: 6.
Total expected deaths: 2·9.

may not be justifiable to combine the data from all three groups.

The survival curve for groups I and IIIb combined shows a reduction in life expectation, calculated from age 1 year, of about five years (table 6). There is a similar reduction in group II (table 7), but few man years were recorded below the age of 15, so the survival curve starts at that age.

Table 6 *Survival tables: (a) chromatin positive men in categories I and IIIb*

Age (yr)	*Life expectation (yr)*	*Surviving fraction*
1	64·1	100·0 +/− 0·0
5	60·1	100·0 +/− 1·2
10	56·6	97·4 +/− 1·6
15	51·6	97·4 +/− 2·0
20	46·6	97·4 +/− 2·2
25	41·6	97·4 +/− 2·3
30	36·6	97·4 +/− 2·3
35	32·1	96·0 +/− 2·3
40	27·4	95·2 +/− 2·4
45	23·8	90·1 +/− 2·4
50	19·8	86·0 +/− 2·5
55	15·6	82·1 +/− 2·5
60	12·3	72·9 +/− 3·0
65	8·3	66·1 +/− 3·4
70	7·1	40·3 +/− 4·5
(b) Simulated control group		
1	*69·5*	100·0
5	65·8	99·7
10	60·9	99·4
15	56·0	99·2
20	51·3	98·8
25	46·5	98·3
30	41·8	97·7
35	37·0	97·1
40	32·5	95·9
45	27·9	94·6
50	23·9	91·0
55	19·7	87·5
60	16·7	78·6
65	13·2	71·2
70	11·1	56·1

Table 7 *Survival tables: (a) chromatin positive men in category II*

Age (yr)	*Life expectation (yr)*	*Surviving fraction*
15	50·8	100·0 +/− 0·0
20	45·8	100·0 +/− 2·4
25	40·8	100·0 +/− 2·7
30	36·5	98·1 +/− 2·8
35	32·2	96·2 +/− 2·8
40	27·9	94·0 +/− 2·9
45	22·9	94·0 +/− 3·2
50	18·5	91·4 +/− 3·3
55	15·2	82·3 +/− 3·5
60	13·0	67·8 +/− 3·7
65	12·8	46·7 +/− 3·5
70	9·5	40·0 +/− 3·4
(b) Simulated control group		
15	56·3	100·0
20	51·6	99·5
25	46·8	99·1
30	42·0	98·6
35	37·2	98·2
40	32·5	97·2
45	27·9	96·2
50	23·7	92·9
55	19·5	89·6
60	16·3	81·1
65	12·7	73·6
70	10·7	57·2

The model of mortality that has been tested here is that of a proportionate increase in death rate affecting all age groups equally. As can be seen in the age break down, this need not be the case. For the combined groups I and IIIb, no ten year age group shows an increase in mortality significantly different from that of the other ages, even with a one tailed test. However, in group II, there is an increase in deaths in the age group 65–75 which is significantly greater than the increase seen in the other age groups on a two tailed test ($p<0·05$). There are insufficient data to allow us to claim this as a real phenomenon. It may just be the result of the subdivision of the data into too many subgroups. Further follow up will be required to settle this point.

Discussion

We have observed an increase in mortality of about 50% in all individuals with KS excluding those identified because of serious physical illness (group IIIa). This increase in death rate is associated with a loss of expected life span of about five years. The implications of this observation to the general population of KS individuals are influenced by considerations of ascertainment bias, sampling error, loss to follow up, and heterogeneity of the sample.

Few, if any, of the KS individuals included in this study could be described as randomly ascertained. In group I, a proportion were recognised in surveys of sections of the community, which are not known to experience mortality different from that of the general population. The majority in this category were self selected, having presented themselves to their medical practitioners with complaints of gynaecomastia or subfertility. It is likely that there are KS subjects who are unconcerned about prominence of the breasts and are content to be childless. Such individuals are not represented in our sample, but we feel it is unlikely that they would suffer a lesser mortality than other KS subjects. In many respects, category IIIb is very similar to group I. These individuals have presented themselves because of minor physical illness, unlikely to affect mortality, and the diagnosis of KS has been suspected because of the characteristic physical features of the condition. We believe that these two categories together come close to being representative of the KS population at large and are typical of those KS patients who come to the attention of general practitioners and hospital physicians. Ascertainment groups II and IIIa have been subject to selection which may have influenced their survival and risk of mortality. The bias in group IIIa is such that it cannot provide useful information on KS mortality in general. Group II

represents a subgroup of KS individuals whose abnormal behaviour has meant that they have spent some time in mental hospitals and who are likely to be at risk of mortality different from that of other KS individuals. It is therefore surprising that their mortality has been so similar to that of group I. On the basis of this study, there is no reason to conclude that this KS subgroup experiences a significantly different mortality from those ascertained in endocrinology or subfertility clinics, but there are insufficient data to exclude this possibility.

Even when ascertainment bias is negligible, there always exists the possibility of sampling error. Hence, although we have observed a relative mortality of 1·41 in those groups most representative of "normal" KS individuals (groups I and IIIb), we are unable to quote this figure confidently for KS in general. We can state that it is unlikely to be outside the range 1·15–2·48. Similarly, we can state that, for those KS subjects in mental institutions, the range is 1·18–2·16.

For such a protracted study, the losses to follow up are remarkably small. This has been due largely to the diligence with which large numbers of medical practitioners have completed the annual questionnaire. As has been demonstrated, the results of this study are not significantly changed by assuming that all the lost individuals survived to the end of 1983.

Within each ascertainment group, there is considerable karyotypic heterogeneity. The most common karyotype is 47,XXY, and most of the other karyotypes are so rare in the community that it is unlikely that epidemiological data will ever be available for each individually.

The causes of death among the KS patients included in this study and a comparison with expected mortalities from these causes will be described in a later publication.

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Appendix: mathematical formulation

Inter-ascertainment group comparison was performed using an extension of Mantel's concept of exposure to death.[13 14] In any age group, k, if the observed number of deaths in the groups A and B were D_a and D_b and the years at risk Y_a and Y_b, then the "exposure to death" in any age group was defined as:

$$E_a = (D_a + D_b).\frac{Y_a}{(Y_a + Y_b)}$$

The total exposure for each ascertainment group was then found by addition of each age group exposure.

$$E_A = \sum_k E_a$$

The groups can then be compared by the use of the statistic,

$$\chi^2 = \frac{(D_A - E_A)^2}{E_A} + \frac{(D_B - E_B)^2}{E_B}$$

where D_A is the total number of deaths observed in group A, etc.

A survival curve was estimated for each ascertainment group by assuming a death rate in each five year age group equal to the deaths observed in that group (m) divided by the years at risk (y).The surviving fraction (x) at age (n + 1) years is therefore

$$x_{n+1} = x_n e^{-p_n}$$

where p_n is the assumed death rate at age n.

The standard deviation of surviving fraction was calculated from the equation:

$$o^2_{x_{n+1}} = x^2_{n+1} \left[\frac{o^2_{x_n}}{x^2_n} + o^2_{p_n} \right]$$

taking the surviving fraction at the starting age to be 100% and its standard deviation to be zero. The observed mortality should follow a Poisson distribution so the standard deviation of the death rate was

$$o^2_{p_n} = p_n / y_n$$

Approximate 95% confidence limits for the survival curves are taken to be defined by two standard deviations from the calculated surviving fraction.

The calculation of the "normal" survival curve presented a problem. Our group of chromatin positive men were acquired from two populations (England and Scotland) known to have different mortality rates. Further different age cohorts within these populations have been exposed to very different risks. The problem was solved by developing a theoretical control group. As each chromatin positive man was entered into the study, a theoretical man of exactly the same age was acquired into the control group. The control individual suffered precisely the death rate published by the Registrars General in that, if his probability of surviving to enter the k'th age group/calendar year element was x, then his probability of entering the next element was xe^{-pt}, where p is the published death rate and t the length of time he would spend in the element if he did not die.This individual therefore contributes $x(1-e^{-pt})$ deaths to the element and $x(1-e^{-pt})/p$ years at risk. The total number of deaths for the control group in each age group was calculated by summing each individual's contribution. Similarly, the control "years at risk" was calculated by addition. These figures were used to define a survival curve in exactly the same way as for the observed groups. Since the theoretical control group is representative of the population at large (given that it is identical with the observed group in birth date, sex, and geographical area) we can neglect sampling error and so no confidence limits are quoted for the control survival curve.

Expectation of life, at any age, was estimated from the life curve by calculation of the area under the survival curve beyond that age and dividing by the surviving fraction at that age.