Mortality and causes of death in females with extra X chromosomes and males with extra Y chromosomes

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SUMMARY A prospective study of mortality in females with extra X chromosomes and males with extra Y chromosomes is reported. Among the 94 females who survived infancy and were then observed on average for 16 years there were 24 deaths compared with an expected mortality of 10.7. The greater than twofold increase is highly significant ($p < 0.005$). The deaths were due to a variety of diseases but no significant increase from any single cause could be identified. Among 136 males with extra Y chromosomes observed on average for 12 years there were 10 deaths. This number is not significantly greater than the expected 6.4. No increase in mortality from a single cause was observed.

The first woman with an additional X chromosome was described by Jacobs *et al* in 1959.¹ The patient, aged 35 years, had been investigated because of secondary amenorrhoea. Buccal mucosa cells were found to contain two sex chromatin bodies instead of the usual one, and it was confirmed subsequently that, as in most women with double chromatin positive status, this was due to a 47,XXX karyotype.² The menstrual abnormality was probably incidental as no association with disturbances in menstruation or with any clearly defined clinical syndrome has been demonstrated in these women. The chromosome abnormality occurs in about 1 in every 1 000 newborn females.³

The first case of a male with a 47,XYY karyotype was reported in 1961 by Sandberg *et al*.⁴ He was a 44 year old married man, the father of 7 children and a manual worker. When consecutive newborn males were karyotyped it was established that approximately 1 in every 1 000 had an extra Y chromosome, that is, a 47,XYY karyotype.³ In adult males with this anomaly there is no characteristic physical abnormality. They are above average in height,⁵ and their frequency among men admitted to security hospitals because of behavioural disorders is about ten times greater than expected from the birth incidence.^{5,6}

We have reported previously on the mortality in males with additional X chromosomes^{7,8} and in females lacking X chromosome material.⁹ In this paper we describe the mortality rates and the causes of death after the first year of life in female patients with extra X chromosomes and male patients with extra Y chromosomes. All these patients are registered with

the MRC Cytogenetic Registry, set up in Edinburgh in 1959 in order to observe prospectively the mortality in patients with sex chromosome aneuploidy.

Patients and methods

The patients included in the study were ascertained between 1960 and 1984. They were notified to the Registry from all parts of the United Kingdom but mainly from Scotland and the north of England. A total of 108 females with extra X chromosomes and 141 male patients with an extra Y chromosome have been registered and followed up. Fourteen females and five males have been omitted from the study because their ascertainment was directly related to illnesses that would have influenced their mortality risk. For the purpose of these studies we have divided the subjects into two categories according to mode of ascertainment: (I) those identified in psychiatric and mental subnormality hospitals or penal establishments in the course of specially designed cytogenetic surveys; (II) those identified in cytogenetic surveys of sections of the general (non-institutionalised) population. Hospital surveys carried out between 1960 and 1971 included all females, and males over 177cm in height at mental subnormality hospitals in Scotland and the north of England and in psychiatric hospitals in the Lothian area. Surveys of resident populations at the four maximum security hospitals in the United Kingdom and new admissions to these hospitals between 1965 and 1981 included all male patients. Surveys in penal establishments covered all new entrants to the allocation centre at Saughton

Table 1 Age at ascertainment

Ascertainment category	Age at ascertainment (yr)							
	1-14	15-24	25-34	35-44	45-54	55-64	65-74	75 +
<i>Females with extra X chromosomes</i>								
I 'Institutions'	0	11	7	5	10	7	5	2
II General population	34	2	2	4	1	3	1	0
<i>Males with extra Y chromosomes</i>								
I 'Institutions'	3	40	31	8	11	2	2	0
II General population	24	4	8	1	1	0	1	0

Prison, Edinburgh, in 1967, cross-sectional studies at two young offenders' institutions in Scotland, male prisoners over 180cm in height in all Scottish prisons, and all males at a Scottish Borstal institution and approved schools between 1966 and 1978. Surveys of the general population included consecutive newborn babies in Edinburgh and district maternity hospitals between 1959 and 1979, a five year old intake to Edinburgh and district schools in 1963, approximately 10 000 adult patients enrolled with five National Health Service group practices in the north of Edinburgh between 1970 and 1978, and males attending Edinburgh subfertility clinics from 1968 to 1981. Females with extra X chromosomes were identified in buccal smear surveys and chromosome surveys, males with extra Y chromosomes in chromosome surveys alone. The ages at ascertainment in the two categories are shown in table 1, the cytogenetic abnormalities in table 2.

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, from date of registration to date of exit from the study, have been calculated and broken down by calendar year, age, and geographical area of ascertainment (England and Wales versus Scotland). A cumulative three-dimensional matrix for each ascertainment category

has been calculated by addition of the individual matrices. The expected number of deaths from each cause has been calculated by multiplication of each element of the cumulative matrix by the relevant published mortality rates. Where the mortality rates are not yet available we have assumed rates identical with those most recently published. The expected and observed deaths, by age group and for all ages, have been compared by the method presented by Liddell.¹⁰

Results

FEMALES WITH ADDITIONAL X CHROMOSOME
Among 94 females with additional X chromosomes there were 24 deaths in 1491 years at risk, 756 in category I and 735 in category II. Nineteen deaths were in category I patients and five deaths in category II. The expected deaths were 8.8 and 1.9, and the corresponding observed mortality ratios (MR) 2.2 (95% confidence limit 1.2-3.3) and 2.6 (95% confidence limit 0.8-5.5) respectively (table 3). There is therefore a greater than twofold increase in mortality overall ($0.0005 < p < 0.001$) and in each category ($0.001 < p < 0.005$; $0.025 < p < 0.05$). The causes of death were cerebrovascular disease (7), cardiovascular disease (6), respiratory disease (6), malignancy (3), schizophrenia (1), and gastrointestinal disorders (1). No significant departure from the expected number of deaths from these causes could be demonstrated.

MALES WITH EXTRA Y CHROMOSOMES
Among 136 males with extra Y chromosomes there were 10 deaths in 1679 years at risk, 1234 in category I and 449 in category II. Nine deaths were in category I subjects and one death in category II. The expected deaths were 5.7 (MR = 1.6; confidence limits 0.7-2.8) and 0.7 (table 4). No significant difference in mortality was therefore observed in either category or overall ($0.2 < p < 0.01$). The causes of death were: respiratory disease (3), cardiovascular disease (3), violent causes (2), malignant disease (1), and anaemia (the cause of

Table 2 Cytogenetic abnormalities

<i>'Karyotype'</i>	<i>Ascertainment category</i>		<i>Total</i>
	<i>I</i>	<i>II</i>	
<i>Females with extra X chromosomes</i>			
47,XXX	40	38	78
46,XX/47,XXX	4	3	7
Chr + +ve	1	6	7
48,XXXX	2	0	2
<i>Males with extra Y chromosomes</i>			
47,XYY	92	35	127
<i>Mosaics:</i>			
46,XY/47,XYY	4	3	7
45,X/46,XY/47,XYY	0	1	1
45,X/48,XYYY	1	0	1

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Table 3 Years at risk for females with extra X chromosomes

(a) Category I (no. of individuals=47)

Calendar year	Age (years)								
	1-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	> 85
1960-64	2.6	13.9	19.2	15.0	18.9	15.1	15.0	4.7	0.0
1965-69	5.0	18.4	32.5	31.9	33.9	34.2	18.1	13.0	0.0
1970-74	0.0	16.4	33.3	29.6	37.1	32.9	19.2	4.0	0.0
1975-79	0.0	9.1	32.5	32.5	31.5	27.6	20.8	6.6	0.0
1980-84	0.0	0.0	22.4	30.3	28.6	32.9	17.7	12.5	0.0
1985-89									
Total	7.6	57.8	140.3	140.1	150.1	142.7	90.8	40.8	0.0
Deaths									
Observed	0	0	1	1	1	4	5	7	0
Expected	0.0	0.0	0.1	0.3	0.7	1.8	2.7	3.2	0.0

Total observed deaths: 19

Total expected deaths: 8.831

(b) Category II (no. of individuals=47)

Calendar year	Age (years)								
	1-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	> 85
1960-64	31.7	0.0	2.0	4.4	2.5	0.0	0.0	0.0	0.0
1965-69	83.5	3.8	0.0	13.0	7.0	4.0	0.0	0.0	0.0
1970-74	105.4	9.0	2.9	5.6	14.4	10.3	5.7	0.0	0.0
1975-79	78.2	62.6	9.7	0.9	15.6	5.5	11.3	0.0	0.0
1980-84	82.9	82.6	12.1	7.9	3.3	7.2	6.0	4.0	0.0
1985-89	14.3	14.4	5.7	3.0	0.0	1.0	1.0	1.0	0.0
Total	396.0	172.3	32.3	34.6	42.9	27.9	24.1	5.0	0.0
Deaths									
Observed	0	0	0	0	1	3	1	0	0
Expected	0.1	0.1	0.0	0.1	0.2	0.3	0.7	0.4	0.0

Total observed deaths: 5

Total expected deaths: 1.882

the anaemia was not specified on the death certificate but is believed to have been due to myelofibrosis).

Discussion and comments

Most of the subjects included in this study have not been randomly ascertained, but individuals known to be at increased risk of mortality because of ascertainment have been excluded. A large proportion of the women in category I have spent much of their lives in hospitals for the mentally subnormal, and this could account for an increase in the number of deaths from diseases of the respiratory system which are known to be three to five times more frequent among the mentally subnormal.¹¹ This would not, however, account for the increased mortality in the female group as a whole. No other single cause of death could be identified to explain the increase.

In sharp contrast to the increased mortality among females and males^{7 8} with extra X chromosomes, no increase could be demonstrated in males with extra Y chromosomes. A greater number of deaths from violent causes might be anticipated in view of the association of this cytogenetic abnormality with antisocial and sometimes violent behaviour, and the high proportion of subjects ascertained in maximum security hospitals, but no increase in deaths of this kind is evident so far in this study.

We are grateful to all the general practitioners and hospital consultants who have assiduously returned the annual questionnaire; to Mrs Anna Frackiewicz and other past members of the registry staff; and to all past and present colleagues in the MRC Clinical and Population Cytogenetics Unit who have helped to gather information about registered patients.

Table 4 Years at risk for females with extra X chromosomes

(a) Category I (no. of individuals=97)

Calendar year	Age (years)								
	1-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	>85
1960-64	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1965-69	4.1	28.5	25.1	13.4	17.0	3.5	0.7	0.0	0.0
1970-74	4.8	88.9	59.3	38.3	32.5	21.4	8.1	0.0	0.0
1975-79	0.2	110.4	124.8	62.9	26.8	33.5	7.1	0.0	0.0
1980-84	0.0	55.6	179.3	96.9	47.2	37.0	9.4	0.0	0.0
1985-89	0.0	4.7	35.2	22.2	14.1	6.4	3.5	0.8	0.0
Total	9.2	288.2	433.8	233.8	137.6	101.8	28.8	0.8	0.0
Deaths									
Observed	0	1	0	1	1	2	4	0	0
Expected	0.0	0.3	0.5	0.5	1.0	2.0	1.4	0.1	0.0

Total observed deaths: 9

Total expected deaths: 5.737

(b) Category II (no. of individuals=39)

Calendar year	Age (years)								
	1-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	>85
1960-64	0.0	1.4	0.8	0.0	0.0	0.0	0.0	0.0	0.0
1965-69	1.8	1.6	5.0	0.0	0.0	0.0	0.0	0.0	0.0
1970-74	48.6	1.8	24.5	3.2	0.0	0.0	2.6	0.0	0.0
1975-79	84.6	3.4	24.0	26.0	0.8	0.0	1.2	0.0	0.0
1980-84	103.9	10.8	11.5	41.5	8.9	0.0	0.0	0.0	0.0
1985-89	15.1	8.4	1.0	7.6	5.0	0.0	0.0	0.0	0.0
Total	254.0	27.3	66.7	78.3	14.7	0.0	3.8	0.0	0.0
Deaths									
Observed	0	0	0	0	0	0	1	0	0
Expected	0.1	0.0	0.1	0.2	0.1	0.0	0.2	0.0	0.0

Total observed deaths: 1

Total expected deaths: 0.731

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