Causes of death in X chromatin positive males (Klinefelter's syndrome)

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SUMMARY The causes of death in 466 X chromatin positive males (Klinefelter's syndrome) studied prospectively over the last 25 years have been analysed. We have previously reported the overall mortality to be increased by 50% and life expectancy reduced by about five years. A highly significant increase in mortality from cerebrovascular disease was observed in the sub group considered to be most representative of X chromatin positive males in general. In the age group up to 45 years this increase could be attributed to deaths from subarachnoid haemorrhage. An increase in mortality from respiratory diseases was observed in those ascertained in psychiatric hospitals. In the sample as a whole there were small but highly significant numbers of deaths from carcinoma of the breast and aortic valve disease. The deaths from carcinoma of the breast were comparable with those expected if female mortality rates were applied.

We have previously reported an increase in mortality of about 50% in males with a positive nuclear X chromatin (Klinefelter's syndrome). The observation was based on 466 males studied prospectively over the last 25 years.¹ The increased mortality was associated with a loss of about five years in lifespan. There was no convincing evidence that the increase in mortality was concentrated in any particular age group or that it was related to the way in which the men had been ascertained. In this paper we analyse the causes of death.

A positive nuclear X chromatin pattern occurs in about 1 or 2 per thousand of the male population. These males have at least one supernumerary X chromosome. During adult life the great majority are infertile and have very small testes. There is an absence of sperm in the seminal fluid and a proportion, about 30%, have gynaecomastia. It is common practice to refer to the condition as Klinefelter's syndrome (KS), but only a minority conform to the original description by Klinefelter and his colleagues. Affected males may present in adult life because of infertility, gynaecomastia, or one of the other clinical features. They may also be identified at any age in the course of nuclear sexing surveys.

Methods

The X chromatin positive males included in the study have been reported to a register of subjects with

chromosome abnormalities which was set up in Edinburgh by the late Professor W M Court-Brown in 1959. The patients have been notified from all parts of the UK but particularly from Scotland and the north of England. A total of 532 chromatin positive males have been followed up since registration. For the purpose of these studies we have divided them into four groups by mode of ascertainment:

- I patients referred because of hypogonadism, gynaecomastia, and subfertility to endocrinology and subfertility clinics and those identified in cytogenetic surveys of sections of the general (non-institutionalised) population;
- II patients identified in psychiatric hospitals in the course of routine clinical and cytogenetic assessment, or in specially designed surveys of such hospitals;
- III patients found incidentally to have features of Klinefelter's syndrome 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 leading to hospital attendance was likely to cause a reduction in life-span (group IIIa) or not (group IIIb).

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, so we feel that it is reasonable to combine the data from these groups to

assess the risk from individual causes of death to KS patients in the general population. The chromosome constitution of the patients in each group has been described elsewhere.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 (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 group 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 for that disease. 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.² As our main objective was to identify an increase in mortality in each of the disease categories examined we have employed a one-tail test. If a two-tail test were employed the p values would be doubled. We have tabulated the analysis for the following major causes of death: diseases of the circulatory system, all neoplasms, diseases of the respiratory system, and all violent causes in each of the ascertainment groups, I/IIb and II. We have also tabulated the deaths and analyses in the following subcategories: cerebrovascular disease, ischaemic heart disease, and neoplasms of the trachea, bronchus, and lung. For the analysis of deaths from carcinoma of the breast and aortic valve disease we have combined the data in groups I, II, and IIb. The international classification of diseases (ICD) rubric numbers are shown in the tables.

Results

The 66 individuals in group IIIa experienced 35 deaths, which is far in excess of an expected figure of 9.7. In view of the totally biased mode of ascertainment with respect to mortality this group has been excluded from further analysis.

The years at risk in the combined group I/IIb and in group II are shown in tables 1 and 3 respectively. Group II is older, 25% of the years at risk being in the age groups over 54 compared with less than 8% in group I/IIb. The expected number of deaths for major disease categories and subcategories, the observed, the probability of the observed for each age group and for all ages are shown in tables 2 and 4. In ascertainment group I/IIb the deaths from cerebrovascular disease were greatly increased at a significance of less than 0.0001. The increase was evident throughout the age range 25-84 years. The three deaths in the younger age group 25-44 were due to subarachnoid haemorrhage and rupture of berry aneurysms. In a fourth patient aged 42 years the cause of death was registered as "cerebral haemorrhage" but at post-mortem examination a diagnosis of subarachnoid haemorrhage was made. In group II a significant increase was observed in deaths from disease of the respiratory system at a probability of less than 0.05. No increase in deaths from cerebrovascular disease was observed.

A comparison of observed and expected deaths from carcinoma of the breast (for women) and from aortic valve disease is shown in table 5. Mortality from carcinoma of the breast is not significantly different from that experienced by women. Deaths from aortic valve disease were very considerably greater than expected.

The registered cause of death, the ICD rubric number of the cause of death included in this study, the registry number, and the age at death of each patient are shown in the Appendix.

Table 1 Years at risk for males in groups I and IIIa (No. of individuals = 309)

Calendar year	Age (years)								
	1-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	>85
1960-64	38.5	74.3	123.7	56.1	21.7	6.0	1.3	0.0	0.0
1965-69	119.9	140.7	197.8	219.4	61.4	28.0	4.6	0.0	0.0
1970-74	141.3	153.2	276.3	301.2	141.4	45.7	14.1	0.4	0.0
1975-79	120.4	120.7	321.9	292.5	243.6	62.3	33.1	7.8	0.0
1980-84	115.5	131.1	255.3	338.9	290.3	127.8	24.1	10.8	0.4
Total	535.7	620.0	1175.0	1208.1	758.4	269.8	77.1	19.0	0.4
% of total	11.5	13.3	25.2	25.9	16.3	5.8	1.7	0.4	

Table 2 Mortality of chromatin positive males in ascertainment groups I* and IIIb† by age and cause of death.

		Age (years)									All ages
Cause of death (ICD rubric nos 1960-66; 1967-)		1-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	>85	
Diseases of the circulatory system (400-468; 390-458)	Observed	0	0	1	5	3	5	6	1	0	21
	Expected p	0.0	0.0	0.2	1.2	3.0	2.9	2.2	1.2	0.0	10.76 <0.01
Ischaemic heart disease (420; 410-414)	Observed	0	0	0	2	1	3	3	0	0	9
	Expected p	0.0	0.0	0.1	0.7	1.7	1.4	1.0	0.4	0.0	5.38 ns
All cerebrovascular disease (330-334; 430-438)	Observed	0	0	1	3	1	1	2	1	0	9
	Expected p	0.0	0.0	0.1	0.1	0.3	0.4	0.4	0.2	0.0	1.52 <0.0001
All neoplasms (140-239; 140-239)	Observed	0	0	0	0	2	1	5	0	0	8
	Expected p	0.0	0.1	0.2	0.6	1.5	1.6	1.1	0.4	0.0	5.68 ns
Neoplasms trachea bronchus, lung (162;)	Observed	0	0	0	0	2	1	2	0	0	5
	Expected p	0.0	0.0	0.0	0.2	0.7	0.7	0.5	0.2	0.0	2.25 ns
All violent causes (800-999; 800-999)	Observed	1	0	1	2	1	0	0	0	0	5
	Expected p	0.1	0.4	0.7	0.8	0.6	0.2	0.1	0.0	0.0	2.90 ns

*Group I: Patients referred, because of hypogonadism, gynaecomastia and subfertility, to endocrinology and subfertility clinics and those identified in cytogenetic surveys of sections of the general (non-institutionalised) population.

†Group IIIb: Patients found incidentally to have features of Klinefelter's syndrome and chromatin positive nuclear sex during the course of clinical assessment in general hospital wards and clinics for non life-threatening disorders.

Table 3 Years at risk for males in group II (No. of individuals = 137)

		Age (years)							
Calendar year	1-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	>85
1960-64	14.8	30.7	27.2	25.0	19.4	18.3	6.1	8.1	0.0
1965-69	17.3	84.6	45.1	58.1	65.7	51.0	26.6	10.2	0.5
1970-74	5.3	72.7	102.0	66.2	102.8	66.5	44.3	9.5	0.0
1975-79	0.2	74.6	178.4	94.6	96.3	88.2	50.0	14.3	4.8
1980-84	0.0	28.4	159.7	156.5	85.0	90.2	42.9	15.0	1.1
Total	37.5	291.0	512.4	400.4	369.1	314.2	169.9	57.0	6.3
% of total	1.7	13.5	23.7	18.6	17.1	14.6	7.9	2.6	0.3

Discussion and comment

The great majority of patients included in this study have not been randomly ascertained, but patients known to be at increased risk because of mode of ascertainment (group IIIa) have been excluded from the study.

The patients in group I/IIIb are younger than those in group II. We have previously recorded that the mortality is increased in both. The numbers of deaths observed from all the causes examined were greater than expected, but with the numbers available we were able to demonstrate significant increases in death from only four of these. Deaths due to

cerebrovascular diseases were increased in group I/IIIb and deaths from respiratory diseases were increased in group II. The deaths from cerebrovascular disease were very strikingly increased, and the deaths occurred throughout the age range 25-84. Rupture of a berry aneurysm was identified as a cause in three⁴ and these deaths were in men aged 25-44 years. Intracranial haemorrhage from ruptured berry aneurysm has been recorded previously in KS patients,^{5,6} but hitherto it has not been a recognised hazard. Patients in group II have spent time in mental hospitals because of disturbed behaviour. This may explain the increased number of deaths from diseases of the respiratory system which

Table 4 Mortality of chromatin positive males in ascertainment group II* by age and cause of death.

		Age (years)									
Cause of death (ICD rubric nos. 1960-66; 1967-)		1-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	>85	All ages
Diseases of the circulatory system (400-468; 390-458)	Observed	0	0	0	0	2	4	7	4	0	17
	Expected p	0.0	0.0	0.1	0.4	1.4	3.4	4.8	4.2	0.5	14.8 ns
Ischaemic heart disease (420; 410-414)	Observed	0	0	0	0	0	2	2	1	0	5
	Expected p	0.0	0.0	0.0	0.2	1.0	2.1	2.5	1.5	0.3	7.71 ns
All cerebrovascular disease (330-334; 430-438)	Observed	0	0	0	0	0	2	1	2	0	5
	Expected p	0.0	0.0	0.0	0.0	0.2	0.5	1.0	1.1	0.3	3.04 ns
Disease of the respiratory system (470-527; 460-519)	Observed	0	0	0	0	2	3	2	3	1	11
	Expected p	0.0	0.0	0.0	0.0	0.3	0.6	1.5	1.3	0.1	3.93 p<0.003
All neoplasms (140-239; 140-239)	Observed	0	0	0	0	0	5	1	1	0	7
	Expected p	0.0	0.0	0.1	0.2	0.8	2.0	2.4	1.3	0.1	6.97 ns
Neoplasms trachea bronchus, lung (162;)	Observed	0	0	0	0	0	3	1	0	0	4
	Expected p	0.0	0.0	0.0	0.0	0.4	0.9	1.1	0.4	0.0	2.84 ns
All violent causes (800-999; 800-999)	Observed	0	0	0	1	0	2	1	0	0	4
	Expected p	0.0	0.2	0.3	0.2	0.2	0.2	0.2	0.2	0.00	1.52 ns

*Group II: Patients identified in psychiatric hospitals in the course of routine clinical and cytogenetic assessment, or in specially designed surveys of such hospitals.

Table 5 Mortality from carcinoma of the breast and aortic valve disease in chromatin positive males in ascertainment groups I, II, and IIIb

		Age (years)		
Cause of death (ICD rubric nos.)		up to 54	55 and over	All ages
Carcinoma of breast (Male 175, Female 174)	Observed	0	2	2
	Expected (female) p	1.15	1.06	2.21 ns
Aortic valve disease (395)	Observed	3	0	3
	Expected p	0.04	0.19	0.23 <0.002

are known to be three to five times more frequent among the mentally subnormal than in the general population.³ There is no satisfactory explanation for the discrepancy between the mortality from cerebrovascular disease in the two groups. Because the numbers available are limited we cannot exclude the possibility that the difference is due at least partly to the different age structure of the groups.

No significant excess of deaths due to neoplasms was recorded in either group but a death from carcinoma of the breast occurred in each. These two deaths are greatly in excess of the expected number for men and similar to the number expected for women (table 5). This observation is consistent with

the previously reported high incidence of carcinoma of the breast in KS patients.^{7,8}

Only one of the three deaths from aortic valve disease was specified as rheumatic. The three deaths are greatly in excess of those expected from aortic valve disease due to all causes (table 5). There is no indication of the reason for an association of disease of the aortic valve with KS from examination of the clinical records of these men. Fricke *et al*⁹ have suggested a defect of collagen as an explanation of an increased incidence of mitral valve prolapse. The same may be true of the aortic valve but no defect of collagen has yet been demonstrated.

Addendum

Since this analysis was completed there has been another death from subarachnoid haemorrhage (aged 55 years) in this series.

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Appendix

Reg. No.	Age (yr)	Yr of death (place of death; S-Scotland E-England)	Registered causes of death	ICD rubric No. of cause of death selected for analysis
<i>Groups I and IIb</i>				
61017	6	1966 E	Ia 'drowning, accidental death'	N994.1
69163	30	1983 S	Ia 'smoke inhalation and burns'	N949
61092	34	1977 S	Ia 'subarachnoid haemorrhage, b rupture of congenital aneurysm of basilar artery'	430
72017	39	1981 E	Ia 'bronchial pneumonia, immobility, cerebral infarction'	438
70306	42	1977 S	Ia 'cerebral haemorrhage'	431
59004	43	1977 E	Ia 'subarachnoid haemorrhage due to ruptured berry aneurysm'	430
61031	43	1981 S	Ia 'coronary thrombosis, II bronchitis and emphysema'	410
66093	44	1974 E	Ia 'myocardial fibrosis'	410
70277	44	1979 E	Ia 'inhalation of vomit due to b alcohol poisoning misadventure'	N980.9
60044	45	1979 E	Ia 'multiple injuries, road traffic accident'	E814
60214	46	1976 S	Ia 'asphyxia, b hanging'	E913.9
63021	47	1972 S	Ia cause of death per precognition 'cerebral thrombosis' resultant on atherosclerosis, per verdict of jury'	433.9
62029	48	1973 S	Ia 'carcinomatosis, b carcinoma of the bronchus'	162.1
67358	50	1972 S	Ia 'acute ventricular failure, b bilateral ventricular hypertrophy, c aortic stenosis'	395.9
68036	53	1969 E	Ia 'acute left ventricular failure, due to b aortic valve incompetence, due to c chronic rheumatic heart disease'	395.0
65077	54	1975 S	Ia 'multiple secondaries in brain & liver b primary carcinoma of bronchus, II Klinefelter's syndrome'	162.1
60045	55	1970 E	Ia 'myocardial infarction'	410
69057	56	1982 E	Ia 'acute congestive cardiac failure, b hypertensive heart disease, and coronary artery disease'	412.0
64111	57	1974 E	Ia 'myocardial infarction, II cerebrovascular accident'	410
64222	57	1979 S	Ia 'bronchogenic carcinoma, II Klinefelter's syndrome, chronic bronchitis'	162.1
64224	58	1981 S	Ia 'coronary insufficiency, b ischaemic heart disease, II obesity'	411
61068	61	1962 S	Ia 'coronary thrombosis' 21 days	420.1
62096	64	1967 E	Ia 'bronchopneumonia, b right hemiplegia'	438

*Post-mortem examination carried out.

†Diagnosis at post-mortem examination: subarachnoid haemorrhage.

continued

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Reg. No.	Age (yr)	Yr of death (place of death; S—Scotland E—England)		Registered causes of death		ICD rubric No. of cause of death selected for analysis
Group I and IIIb—continued						
60007	66	1978	S	Ia b c II Ia b Ia	'acute myocardial infarction, congestive cardiac failure, chronic obstructive airways disease, obesity, Klinefelter's syndrome' 'coronary thrombosis, arteriosclerosis' 'bronchopneumonia, due to multiple myelomatosis'	410 410 203
61096	67	1962	E	Ia II	'carcinoma of breast, congestive cardiac failure'	174
61040	69	1978	S	Ia II	'cerebro-vascular accident, congestive cardiac failure'	436
61059	70	1979	S	Ia	'bronchogenic carcinoma'	162.1
67223	71	1977	E	Ia	'carcinoma head of pancreas**	157.9
78033	71	1978	S	Ia b II	'bronchopneumonia, bronchogenic carcinoma, metastases to brain and right foot'	162.1
61056	72	1977	S	Ia b c	'myocardial degeneration Parkinson's disease, general arteriosclerosis'	412
78096	72	1979	S	Ia b	'cerebral haemorrhage, cerebral atherosclerosis'	431
74145	75	1982	S	Ia b c	'cerebro-vascular accident, generalised arteriosclerosis, hypertension'	436
Group II						
64060	29	1969	S		'sub acute hepatic necrosis**	570
69041	32	1973	E	Ia II	'status epilepticus, severe subnormality'	345.2
73070	36	1978	E	Ia	'severe burns**	N949
60235	49	1979	S	Ia II	'bronchopneumonia, mental deficiency'	485
65064	51	1972	E	Ia b II	'cardiac failure, aortic stenosis, Klinefelter's syndrome'	395.9
73073	51	1980	E	Ia b	'bronchopneumonia, aplastic anaemia'	284
60186	53	1976	S	Ia b c II	'bronchopneumonia, atrial fibrillation, atrial septal defect, Klinefelter's syndrome, mental deficiency**	746.4
68133	54	1971	E	Ia b II	'acute respiratory failure, chronic bronchitis, diabetes mellitus, Klinefelter's syndrome'.	491
65059	56	1968	E	Ia b II	'left ventricular failure, coronary thrombosis Klinefelter's syndrome'	410
60115	57	1979	S	Ia II	'bronchial carcinoma' Klinefelter's syndrome, mental deficiency	162.1
63024	57	1969	S	Ia II	'drowning, chronic alcoholism'	N994.1
65076	57	1977	S	Ia	'carcinoma anus, multiple metastasis'	173.6
67339	57	1978	E	Ia	'coronary thrombosis**	410
68013	58	1968	S	Ia b c	'pulmonary embolism, emphysema, chronic bronchitis'	491
60091	60	1968	E	Ia b	'pulmonary embolus, deep vein thrombosis**	451.0
64159	60	1965	S	Ia b II	'haemoptysis, bronchial carcinoma, schizophrenia**	162.1
65058	61	1978	E	Ia b	'bronchopneumonia, cerebral infarct with right hemiplegia'	438

*Post-mortem examination carried out

†Post-mortem examination: adenocarcinoma of colon (additional finding)

continued

Reg. No.	Age (yr)	Yr of death (place of death; S-Scotland E-England)	Registered causes of death		ICD rubric No. of cause of death selected for analysis	
Group II—continued						
61114	62	1975	S	Ia b c II	'bronchopneumonia, immobilisation, fractured femur, pinned and plated, parkinsonism'	N821.0
67396	62	1983	E	Ia b II	'disseminated lymphoma, primary lymphoma, Milroys disease**	202.2
68129	62	1983	E	Ia b II	'bronchopneumonia, chronic obstructive airways disease, chronic schizophrenia'	491
61137	63	1961	S		'bronchopneumonia, 1 day nephrosis, 1 year hemiplegia' 1 month	434
63031	63	1979	S	Ia b II	'carcinomatosis, carcinoma breast, symptomatic epilepsy, Klinefelter's syndrome'	174
64181	64	1981	E	Ia	'left basal bronchopneumonia'	485
68089	64	1975	S	Ia	'bronchial carconoma'	162.1
61089	65	1975	S	Ia b c	'bronchopneumonia, ischaemic vascular disease, aortic thrombosis**+	444.1
61090	67	1980	S	Ia b	'bronchopneumonia, congestive cardiac failure'	427
73082	67	1979	E	Ia	'carcinoma bronchus'	162.1
63012	70	1969	S	Ia b c	'congestive cardiac failure, bronchopneumonia, chronic interstitial fibrosis'	517
65052	73	1974	E	Ia b II	'congestive cardiac failure, arteriosclerosis, mental subnormality'	440.9
65075	73	1977	E	Ia b	'congestive cardiac failure, cardiovascular degeneration'	412.9
60237	74	1980	S	Ia b	'natural causes, suspected myocardial degeneration'	412.9
61113	74	1978	S	Ia II	'cerebrovascular accident, arteriosclerotic dementia, chronic schizophrenia'	438
63030	74	1982	S	Ia b c	'bronchopneumonia, immobilisation, fracture neck of femur'	N821.0
60243	75	1979	S	Ia b II	'cardiorespiratory failure, anaemia, Klinefelter's syndrome'	590.1
75270	75	1979	E	II Ia b c II	'old myocardial infarction, intracardiac aneurysm** 'bronchopneumonia, heart failure, chronic bronchitis, mental subnormality'	491
67393	76	1980	S	Ia b c II	'coronary thrombosis, cardiac ischaemia, senile vascular degeneration' manic depressive psychosis'	410
61091	77	1964	S	Ia b c II	'peritonitis, perforated gastric ulcer, large chronic gastric ulcer, pyelonephritis, cerebral thrombosis**	531.0
62028	78	1965	S	Ia b	'cerebral haemorrhage, cerebral arteriosclerosis'	431.9
63013	78	1965	S	Ia b c II	'generalised circulatory insufficiency, haemorrhage from peptic ulceration, cardiovascular degeneration, chronic bronchitis, mental deficiency'	422.1
62027	79	1978	S	Ia II	'bronchopneumonia, delusional insanity'	485
62043	79	1972	S	Ia b	'bronchopneumonia, cerebral arteriosclerosis'	437.9
61177	81	1965	S	Ia II	'bronchopneumonia, left side cardiac failure'	485
62020	86	1964	S	Ia	'bronchopneumonia'	485
61115	90	1979	S	Ia II	'bronchopneumonia, chronic schizophrenia, Klinefelter's syndrome'	485

*Post-mortem examination carried out

†Post-mortem examination: adenocarcinoma of colon (additional finding)