Mortality ratios, life expectancy, and causes of death in patients with Turner's syndrome

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SUMMARY  In a prospective study of 156 female patients with Turner's syndrome who had survived infancy and been followed up for an average of 17 years there were 15 deaths. The expected mortality was 3-6. Sixteen of the patients had a congenital heart anomaly and five of the deaths occurred in this group. The 10 deaths in the remaining 140 were three times as many as expected. The reduction in life expectation was 12-5 years at age 1 year, 11 years at age 20, and 10 years at age 40. Deaths were due to a broad spectrum of diseases. In the sample as a whole there were eight deaths from diseases of the circulatory system. This number is significantly greater than expected, but four were due to congenital heart disease. When patients with congenital heart disease were omitted from the sample the mortality from circulatory disorders was not significantly increased. Within the category of circulatory disorders there were three deaths from dissection of the aorta, a number which is greatly in excess of the expected. Two of these patients had no previous evidence of heart disease.

Turner's syndrome is a condition in females which is characterised by short stature, gonadal dysgenesis, and a number of congenital morphological abnormalities. Because of the failure of gonadal development there is little or no sexual maturation at the age of puberty and a large proportion of patients are ascertained on this account. At an earlier age attention may be drawn to the condition because of failure to grow, congenital heart disease, and such morphological abnormalities as redundant folds of skin in the neck (pterygium coli), lymphangiectatic oedema, deformities of the ears, dystrophic nails, shortening of the metacarpals, cubitus valgus, ptosis, strabismus, and pigmented naevi. Many of the congenital deformities were noted in infants by Ulrich in 1930, but the failure of normal sexual development at puberty was not emphasised until the condition was described in a series of young women by Turner in 1938. In most patients the syndrome can be attributed to partial or complete monosomy of the X chromosome. After early childhood the majority of patients have no recognisable gonadal tissue and the position of the ovaries is occupied by streaks of fibrous tissue. (Exceptionally, follicular cells may persist into adult life, and rare cases of fertility have been described.) Levels of plasma luteinising hormone (LH) and follicle-stimulating hormone (FSH) are elevated above the normal before and after puberty. Plasma oestrogens do not rise above prepubertal levels. Data obtained from the screening of consecutive newborn babies indicate that the incidence at birth is of the order of 3 per 10 000 female live births.

The infant mortality in Turner's syndrome is high. Robinson 4 reported three infant deaths in nine 45,X females identified at birth and two out of four identified by MacLean et al 5 died in infancy. In this paper we describe the mortality after the age of 1 year in a series of patients with Turner's syndrome registered with the MRC Abnormal Karyotype Registry in Edinburgh. This registry was set up in 1959 with the object of observing prospectively the mortality in patients with chromosome abnormalities.

Methods

The patients were ascertained between 1959 and 1984. They were notified to the registry from all parts of the UK but particularly from Scotland and the North of England. They had been identified because they had presented with one or more of the clinical features of Turner's syndrome, or when they were found, during cytogenetic surveys of the newborn and other sections of the general population, to have an abnormal nuclear sex in mucosal cells or a
chromosome abnormality in peripheral blood leucocytes (table 1). A total of 156 patients ascertained in this way have been followed up since registration. (Another nine patients were ascertained when being observed for disorders other than those connected with Turner's syndrome. These disorders could have influenced the survival of the patients so they were omitted from the study.) The patients' ages at ascertainment and their karyotype abnormalities are shown in table 2. All patients had the features of Turner's syndrome. Sixteen suffered from congenital heart disease and the details of these are listed in table 3.

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 Registrar General. For each individual the years at risk, from date of registration to date of exit from the study (death or loss to follow up), 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 has been calculated by addition of the individual matrices (table 4). The expected number of deaths from all causes and from diseases of the circulatory system have been calculated by multiplication of each element of the cumulative matrix by the relevant published mortality rates. Where the mortality rates were not yet available we assumed rates identical with those most recently published. (After an initial examination of the causes of death a comparison was also made between observed and expected deaths from dissection of the aorta.) Congenital heart disease, which is an associated feature in a proportion of patients with Turner's syndrome, carries a significantly increased mortality rate. The data were also analysed with these patients excluded (table 5).

The expected and observed deaths, by age group and for all ages, have been compared throughout by the method presented by Liddell. The life tables were constructed by a method described elsewhere but as were so few years of follow up after the age of 60 years calculation of the surviving fraction beyond this age was not possible. In constructing the life tables, we have assumed therefore that either (a) the mortality of Turner syndrome patients after age 60 years is equal to that of normal females of the same age, or (b) that there is the same increase in relative mortality in Turner patients after the age of 60 years as there is before that age. Separate life expectations predicted by each of these assumptions were calculated from the relevant curves for surviving fractions (table 6).

### Results

There were 15 deaths among the 156 patients observed over the 25 years of the study. The expected mortality in a female UK population of the same size and age structure would be 3.6. There is therefore a very significant increase in mortality (p<0.00001).

### Table 1 Reason for ascertainment

<table>
<thead>
<tr>
<th>Primary reason for ascertainment</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary amenorrhoea</td>
<td>96</td>
</tr>
<tr>
<td>Secondary amenorrhoea or other menstrual irregularity</td>
<td>6</td>
</tr>
<tr>
<td>Retardation of growth</td>
<td>27</td>
</tr>
<tr>
<td>Buccal smear surveys, chromosome surveys (newborn, general population, institutions, etc)</td>
<td>15</td>
</tr>
<tr>
<td>Other features of Turner's syndrome</td>
<td>12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>156</td>
</tr>
</tbody>
</table>

### Table 2 Chromosome abnormality, age at ascertainment, number lost to follow up, and deaths of 156 patients with Turner's syndrome

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Age at ascertainment</th>
<th>Lost to follow-up</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-14</td>
<td>15-24</td>
<td>25-34</td>
</tr>
<tr>
<td>45,X</td>
<td>27</td>
<td>36</td>
<td>11</td>
</tr>
<tr>
<td>46,X,i(Xq)</td>
<td>1</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>46,X,del(X) (p)</td>
<td>-</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Mosaics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45,X/46,XY</td>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>45,X/46,XX</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>45,X/46,X,i(Xq)</td>
<td>2</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>45,X/47,XXX</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>45,X/47,XY</td>
<td></td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>45,X/46,X,del(X) (p)</td>
<td>2</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>45,X/46,X,++</td>
<td>3</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>45,X/46,X,++</td>
<td>1</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>45,X/46,X,+mar</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td>44</td>
<td>79</td>
<td>22</td>
</tr>
</tbody>
</table>
### Table 3 Patients with congenital heart disease

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Congenital heart defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>600252</td>
<td>Atrial septal defect</td>
</tr>
<tr>
<td>610150</td>
<td>Mild aortic stenosis</td>
</tr>
<tr>
<td>620040</td>
<td>Aortic incompetence</td>
</tr>
<tr>
<td>630004</td>
<td>Coarctation of the aorta</td>
</tr>
<tr>
<td>640151</td>
<td>Ventricular septal defect</td>
</tr>
<tr>
<td>650097</td>
<td>Congenital mitral stenosis with pulmonary hypertension</td>
</tr>
<tr>
<td>660061</td>
<td>Patent ductus arteriosus</td>
</tr>
<tr>
<td>670380</td>
<td>Coarctation of the aorta</td>
</tr>
<tr>
<td>670388</td>
<td>Patent ductus arteriosus and coarctation of the aorta</td>
</tr>
<tr>
<td>680094</td>
<td>Coarctation of the aorta</td>
</tr>
<tr>
<td>680204</td>
<td>Mild pulmonary stenosis</td>
</tr>
<tr>
<td>700278</td>
<td>Partial anomalous venous drainage</td>
</tr>
<tr>
<td>730123</td>
<td>Coarctation of the aorta</td>
</tr>
<tr>
<td>770015</td>
<td>Aortic stenosis</td>
</tr>
<tr>
<td>790053</td>
<td>Small aortic septal defect</td>
</tr>
<tr>
<td>790135</td>
<td>Maladie de Roger</td>
</tr>
</tbody>
</table>

Eleven patients in the study were lost to follow up. (If they had remained in the study the expected mortality would have been 3.84.)

Five of the 15 deaths were in patients with congenital heart disease and four of these were a direct consequence of the cardiac abnormality. When patients with congenital heart disease were omitted from the analysis the mortality in the remainder was still three times the expected (p<0.005) and the increase in mortality was evident in each represented age group. (The five deaths among the 16 patients with congenital heart disease compare with an expected number of 0.17.)

When patients with congenital heart disease are excluded from the study and assuming that the

### Table 4 Years at risk—all patients. Deaths, observed and expected, from all causes, circulatory disorders, and dissection of the aorta in 156 patients with Turner's syndrome

<table>
<thead>
<tr>
<th>Calendar years</th>
<th>Age group (years)</th>
<th>Value for p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1–14</td>
<td>15–24</td>
</tr>
<tr>
<td>1960–64</td>
<td>53-7</td>
<td>120-0</td>
</tr>
<tr>
<td>1965–69</td>
<td>73-6</td>
<td>231-6</td>
</tr>
<tr>
<td>1970–74</td>
<td>55-0</td>
<td>181-3</td>
</tr>
<tr>
<td>1975–79</td>
<td>48-4</td>
<td>109-7</td>
</tr>
<tr>
<td>1980–84</td>
<td>40-7</td>
<td>80-8</td>
</tr>
<tr>
<td>Totals</td>
<td>271-4</td>
<td>723-5</td>
</tr>
</tbody>
</table>

Deaths from all causes
- **Observed**
  - 1
  - 4
  - 1
  - 5
  - 1
  - 2
  - 0
  - 1
  - 0
  - 0
  - 15

- **Expected**
  - 0.3
  - 0.6
  - 0.9
  - 0.8
  - 0.4
  - 0.4
  - 0.1
  - 0
  - 0
  - 3-6

Deaths from circulatory diseases
- **Observed**
  - 1
  - 1
  - 1
  - 3
  - 0
  - 2
  - 0
  - 0
  - 0
  - 0
  - 8

- **Expected**
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 1-2

Deaths from aortic dissection
- **Observed**
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0

- **Expected**
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 3

### Table 5 Years at risk—Deaths, observed and expected, from all causes, circulatory disorders, and dissection of the aorta, in 140 patients with Turner's syndrome without congenital heart disease

<table>
<thead>
<tr>
<th>Calendar years</th>
<th>Age group (years)</th>
<th>Value for p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1–14</td>
<td>15–24</td>
</tr>
<tr>
<td>1960–64</td>
<td>47-1</td>
<td>118-0</td>
</tr>
<tr>
<td>1965–69</td>
<td>60-1</td>
<td>219-1</td>
</tr>
<tr>
<td>1970–74</td>
<td>49-1</td>
<td>158-7</td>
</tr>
<tr>
<td>1975–79</td>
<td>48-3</td>
<td>90-6</td>
</tr>
<tr>
<td>1980–84</td>
<td>40-7</td>
<td>64-8</td>
</tr>
<tr>
<td>Totals</td>
<td>245-3</td>
<td>651-3</td>
</tr>
</tbody>
</table>

Deaths from all causes
- **Observed**
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 10

- **Expected**
  - 0.1
  - 0.3
  - 0.6
  - 0.4
  - 0.8
  - 0.4
  - 0.4
  - 0.1
  - 0
  - 3-5

Deaths from circulatory diseases
- **Observed**
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 4

- **Expected**
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 1-2

Deaths from aortic dissection
- **Observed**
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 2

- **Expected**
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
approximate threefold increase in mortality continues after age 60 years, the life expectation is reduced by about 12-5 years at age 1, by about 11 years at age 20, by 10 years at age 40, and 8 years at age 60. (In the unlikely event that mortality reverted to a normal rate at age 60 years the life expectation at age 1 year would be reduced by about 6.5 years, 5 years at age 20 years, and 3.5 years at age 40.) There is therefore a considerable reduction in life expectation in Turner's syndrome even in the absence of congenital heart disease.

The registered causes of death are shown in tables 7a and b. In the series as a whole 8 of the 15 deaths were due to diseases of the circulatory system compared with an expected mortality from this cause of 1·2. Four of the deaths were in the 16 patients with congenital heart disease. In the remainder, the deaths from circulatory diseases are not significantly in excess of the expected (4 versus 1·2; p<0.08). Three of the eight cardiovascular deaths were due to dissection of the aorta and two of these occurred in patients who had no previous evidence of valvular

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at death</th>
<th>Karyotype</th>
<th>Registered cause of death</th>
<th>ICD rubric No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>600033</td>
<td>17</td>
<td>45,X</td>
<td>Ia Uraemia, b Pyo-hydronephrosis, c Uretero-vesical dysfunction</td>
<td>600.0 (7th rev)</td>
</tr>
<tr>
<td>610146</td>
<td>55</td>
<td>45,X/46,X, +mar</td>
<td>Ia Cerebral embolism, b Hypertension</td>
<td>434.0 (8th rev)</td>
</tr>
<tr>
<td>620002</td>
<td>39</td>
<td>45,X</td>
<td>Ia Haemopericardium, due to b Dissecting aortic aneurysm, due to c Turner's syndrome*</td>
<td>441.0 (9th rev)</td>
</tr>
<tr>
<td>630051</td>
<td>42</td>
<td>46,X,i(Xq)</td>
<td>Ia Carbon monoxide (coal gas) poisoning</td>
<td>N968 (7th rev)</td>
</tr>
<tr>
<td>630101</td>
<td>19</td>
<td>45,X/46,X,i(Xq)</td>
<td>Ia Myocardial infarction</td>
<td>410 (9th rev)</td>
</tr>
<tr>
<td>650098</td>
<td>29</td>
<td>45,X/46,X,r(X)</td>
<td>Ia Diabetes mellitus</td>
<td>567 (8th rev)</td>
</tr>
<tr>
<td>650118</td>
<td>20</td>
<td>45,X/46,XY</td>
<td>Ia Peritonitis, b Pelvic abcess</td>
<td>183 (8th rev)</td>
</tr>
<tr>
<td>660087</td>
<td>73</td>
<td>45,X/46,XX/47,XXX</td>
<td>Ia Chronic enteropathy*</td>
<td>590.0 (8th rev)</td>
</tr>
<tr>
<td>680103</td>
<td>43</td>
<td>45,X</td>
<td>Ia Hepatic failure, b Turner's syndrome</td>
<td>573 (8th rev)</td>
</tr>
</tbody>
</table>

Table 7(b) Causes of death, after age 1 year, in 16 patients with Turner's syndrome and congenital heart disease

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at death</th>
<th>Karyotype</th>
<th>Registered cause of death</th>
<th>ICD rubric No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>600252</td>
<td>10</td>
<td>45,X</td>
<td>Ia Acute cardiac failure, b Atrial septal defect, c Turner's syndrome</td>
<td>746.4 (8th rev)</td>
</tr>
<tr>
<td>620040</td>
<td>38</td>
<td>45,X</td>
<td>Ia Dissection of thoracic aorta, b Dilatation of aortic arch, c Turner's syndrome</td>
<td>441.0 (8th rev)</td>
</tr>
<tr>
<td>650097</td>
<td>44</td>
<td>45,X</td>
<td>Ia Right lobar pneumonia</td>
<td>481.0 (8th rev)</td>
</tr>
<tr>
<td>670380</td>
<td>18</td>
<td>45,X</td>
<td>Ia Congestive cardiac failure, b Ischaemic heart disease</td>
<td>747.1 (8th rev)</td>
</tr>
<tr>
<td>700287</td>
<td>57</td>
<td>45,X</td>
<td>Ia Congestive cardiac failure, b Ischaemic heart disease</td>
<td>411 (9th rev)</td>
</tr>
</tbody>
</table>

*Confirmed by postmortem examination
heart disease or disease of the aorta. A fourth patient with mild coarctation of the aorta died of rupture of the aorta. In one patient it was demonstrated at postmortem examination that dissection was due to cystic medial necrosis of the aorta. Congenital heart disease and aortic dissection did not account entirely for the excess mortality in this study, but no other specific single cause of death was identified.

Discussion

The prevalence of Turner's syndrome after the age of 1 year is probably as low as 1 in 20 000–30 000 of the female population and this series could include the majority of patients with this disorder in Scotland and the North East of England. The mortality recorded in the sample is likely therefore to be representative of that experienced by Turner's syndrome patients in general after infancy. One third of deaths occurred in those with congenital heart disease but even among the remainder there was a threefold increase in mortality. It applied throughout the age range covered by the patients in the study, but as the majority of the patients had been ascertained either at birth or at puberty, very few had attained the age of 60 years and we were not able to make any calculations on survival beyond that age. We have calculated the life expectation on the assumptions that mortality continues either at the same threefold increase in rate observed up to age 60, or that it then falls to the same level as that for all women. The threefold increase occurred in patients who had no obvious life threatening congenital abnormality, so we have no reason to believe that the increase in mortality will be any less after age 60. The life expectations based on the first assumption would seem to be the most likely therefore.

Most of the deaths were in patients with a 45,X karyotype but the same relative increase in mortality was observed in those with other karyotype abnormalities.

The incidence of severe congenital cardiovascular disease in Turner's syndrome is high. It accounted for three of the five infant deaths reported by McLean et al. Its prevalence in reported series has varied between 7% and 36%, depending on the method of ascertainment. The most common abnormality is coarctation of the aorta which has been reported in between one-tenth and one-third of all cases. Other forms of congenital heart disease, particularly aortic and subaortic stenosis (either on their own or together with coarctation of the aorta), but also atrial and ventricular septal defects, patency of the ductus arteriosus, dextrocardia, and pulmonary stenosis occur with increased frequency in this condition. Dissection of the aorta is not a widely recognised complication of Turner's syndrome but it has now been reported in at least 12 patients, including those reported in this study. In seven of the 12 the dissection was associated with coarctation of the aorta, although in three of these the coarctation was not haemodynamically significant. Cystic medial necrosis, recognised at postmortem examination in one of our patients and reported previously in association with this syndrome, suggests that there is a defect in the connective tissue of the wall of the aorta similar to that found in Marfan's syndrome. The death due to cerebrovascular disease at age 55 was in a patient who suffered from hypertension, a recognised risk factor, and one of the two deaths from myocardial infarction was in a patient who suffered from diabetes mellitus, which is known to predispose to atherosclerosis. Both hypertension and diabetes mellitus are believed to occur with a higher frequency than normal in patients with Turner's syndrome.14

In the patient who died of peritonitis following a pelvic abscess and a non-specific inflammatory bowel disease the gluten enteropathy reported on the death certificate was not proven. The liability to non-specific inflammatory disease of the bowel in Turner's syndrome has now been reported on a number of occasions. The death registered as due to an ovarian adenocarcinoma occurred in a patient in whom a diagnosis of gonadal dysgenesis had previously been made. It is believed that the carcinoma arose in a gonadoblastoma, a tumour of rudimentary gonadal streaks which contains all the basic cell types entering into the formation of a gonad. In a survey of the literature, Golberg and Scully found that gonadal malignancies occur less often in Turner's syndrome than in other types of gonadal dysgenesis, the exception being the individual with a "XY-mosaic karyotype".15

Congenital renal abnormalities are a common feature of Turner's syndrome. They are usually of a minor nature, for instance, a duplex or horseshoe kidney, but such abnormality may have contributed to the hydronephrosis and ureterovesical dysfunction in patient 600033, although no congenital abnormality had been recognised during life.

Patients 680103 and 700287 had been found during cardiac investigation to have partial anomalous pulmonary venous drainage, an abnormality which is usually of relatively minor haemodynamic significance and not a potential cause of death.

This study confirms that cardiovascular diseases, both congenital and acquired, are the most life-threatening in Turner's syndrome, but other diseases also significantly increase the mortality rate and limit life expectation. Many of the disorders from
which these patients died are now treatable if diagnosed in time. Careful surveillance and awareness of the diseases that are a special hazard for these patients could probably reduce the mortality rate and increase their life expectation.

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

References