Survival in trisomy 13 and trisomy 18 cases ascertained from population based registers

C M Brewer, S H Holloway, D H Stone, A D Carothers, D R FitzPatrick

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Although long term survivors are well documented, infants with the autosomal trisomies 18 (Edwards syndrome) or 13 (Patau syndrome) usually die in the first few days or weeks of life. Accurate estimates of life expectancy are few, particularly in the case of trisomy 13. There have been six population surveys of survival in trisomy 18, comprising 430 unselected cases. In contrast there have been only two such studies of trisomy 13 involving 35 cases. A reliable estimate of survival time is important when counselling parents following a pre- or postnatal diagnosis. The fact that a significant proportion of infants succumb within the first 24 hours is a major contributing factor to the short median survival time. Given this fact, a means of revising the estimate of survival when an infant is already several days old is important. Using information available on infants with trisomy 13 or 18 born in Scotland from 1974 to 1997, we have calculated median survival times in this population and prepared revised figures which take into account continued survival.

PATIENTS AND METHODS

Cases were ascertained from two sources, the Scottish Trisomy Register 1989-1997 and the Glasgow Register of Congenital Anomalies 1974-1989. The Scottish Trisomy Register was established in 1989 and is a database of autosomal trisomies in Scotland; information is collected from the Scottish service laboratories and includes name, date of birth, type of sample, karyotype, and whether liveborn. Dates of death are ascertained separately. The Glasgow Register of Congenital Anomalies is a multisource, population based congenital anomaly database of offspring of mothers resident in the Greater Glasgow Health Board area. Diagnostic validation by trained registry workers is performed on all notified cases. Only liveborn, non-mosaic free trisomies, both pre- and postnatally ascertained, were included in this study. These two sources provide non-overlapping data covering the 24 years from 1974 to 1997 and a check was carried out to ensure that no case was included twice. Median survival for all liveborn infants was calculated (SPSS for Windows version 6.1) and survival curves for the Scottish Trisomy Register and the Glasgow Register of Congenital Anomalies were estimated separately and compared using the Logrank Test. In addition, the Cox proportional hazards model was used to investigate whether there was an association between year of birth and survival for either trisomy. Revised survival times were calculated for infants still alive at 1, 2, 7, 14, and 30 days after excluding those who had already died.

RESULTS

Trisomy 13

There were 26 live births with full trisomy 13 in the Scottish Trisomy Register. In four cases, details were incomplete and dates of death could not be ascertained, so these have been excluded from further analysis. There were 10 cases in the Glasgow Register of Congenital Anomalies, giving a total of 32 cases for analysis. The median survival time was 8.5 days (range 1-412 days). Kaplan-Meier survival curves were plotted for the two datasets separately but no significant difference was found using the Logrank test (data not shown). Since the two databases cover non-overlapping periods, these results indicate there has been no significant secular change in survival during the period of the study. This was further confirmed by the lack of a significant association between year of birth and survival using the Cox Proportional Hazards model. The cases were therefore pooled. Proportions of infants surviving a given time period by time already survived are given in table 1.

Trisomy 18

For infants with trisomy 18, data were complete in 59 out of 63 cases recorded in the Scottish Trisomy Register and in all 25 cases recorded in the Glasgow Register of Congenital Anomalies giving a total of 84 cases for analysis. The median survival was 6 days (range 1-975 days). Kaplan-Meier survival curves were plotted for the two datasets separately, but no significant difference was found using the Logrank test. Using the Cox proportional hazards model, no significant association was found between year of birth and survival. Thus, over the period of study there has been no change in survival in this condition. The cases were therefore pooled. Proportions of infants surviving a given time period by time already survived are given in table 1.

DISCUSSION

The median survival times (MST) calculated in this survey are broadly similar to those of previous population studies. Our
MST of 8.5 days in trisomy 13 is longer than that reported by Wyllie et al (4 days) and by Goldstein and Nielsen (2.5 days). Our MST in trisomy 18 (6 days) is remarkably similar to the other population based studies. Several other studies using selected populations have also been reported. Weber et al found that 98% survived the first day and 8% were still alive at one year based on 192 cases collected from published reports and personal communications. This might be explained by the fact that in the 1960s the diagnosis of chromosome abnormalities was often made much later, by which time many affected babies would have died. Magenis et al used data on trisomy 13 obtained from their own laboratory records, published cases, and from questionnaires to other laboratories and found that 28%, 44%, and 86% had died by the end of the first week, month, and year, respectively, but they did not calculate median survival. Taylor et al reported MST of 89 and 70 days in trisomy 13 and 18 respectively based on data from a population study of 27 cases of each trisomy in south east England combined with 47 trisomy 13 and 126 trisomy 18 published cases. The MSTs reported by Hodes et al (74 days for trisomy 13 and 35 days for trisomy 18) are likely to be biased since these cases were ascertained through a tertiary referral centre and a number of cases may have died before transfer. Similarly, Redheedran et al recognise likely ascertainment bias in the 19 cases of trisomy 13 in which they did not calculate median survival. In this study, the only information known to be missing concerns four cases of each trisomy diagnosed in the same cytogenetics laboratory where, for administrative reasons during a short period of the study, patient names were not notified making it impossible to ascertain dates of death. However, there is no reason to suppose that survival in these particular cases was any different from that in the rest of the cohort.

Although median survival is useful in counselling, our estimates that take into account the survival of the infant to date should prove particularly helpful to parents. In this study, the percentage of deaths which occurred in the first 24 hours was 25% for trisomy 13 and 12% for trisomy 18. The revised figures show a trend for increased survival at 1 week and 1 month for trisomy 13 infants who survive this period, but only in trisomy 18 infants who survive 48 hours. For both trisomies the probability of survival beyond 1 year is small and does not change substantially in infants who have already survived up to 1 month.

It might be expected that advances in prenatal diagnosis and neonatal intensive care would have affected life expectancy. For example, an increase in the use of prenatal diagnosis will result in a lower rate of affected livebirths generally, but may selectively reduce the numbers with significant malformations, since these are more likely to be detected by prenatal ultrasound scan and subsequent karyotyping. This might result in a longer median survival. Similarly, advances in neonatal intensive care and paediatric surgery for infants born with malformations might also prolong survival. However, our results, together with those of other authors since the 1960s, suggest there has been no significant change in survival over the last 20 years. This may be explained by the fact that the most common reported cause of death in both conditions is central apnoea which is difficult to prevent even with modern neonatal intensive care. The most important limitation of this study is that we did not have accurate information on the exact pattern of malformations in the individual cases. We could, therefore, not correlate the presence of severe heart or brain malformations with the timing of early neonatal deaths.

Table 1 Proportions of infants, who have survived a given number of days, by total length of survival. For example, if counselling the parents of an infant with trisomy 13 who has survived for 14 days then there is a 60% (35 to 85% CI) chance that the infant will survive to the age of 1 month and a 7% (0 to 19% CI) chance that they will survive for 1 year. The revised median survival times with confidence intervals which do not overlap with those calculated at birth are marked with an asterisk.

<table>
<thead>
<tr>
<th>Time already survived</th>
<th>Trisomy 13</th>
<th>Observed length of survival (95% confidence limits)</th>
<th>Trisomy 18</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Birth</td>
<td>1 day, 1 week, 1 month, 1 year</td>
<td>Birth</td>
</tr>
<tr>
<td>1 day</td>
<td>75% (60 to 90)</td>
<td>50% (33 to 67) 28% (13 to 44) 3% (0 to 9)</td>
<td>88% (81 to 95) 43% (32 to 53) 25% (16 to 34) 2% (0 to 6)</td>
</tr>
<tr>
<td>2 days</td>
<td>67% (68 to 86)</td>
<td>38% (18 to 57) 4% (0 to 12) 7% (0 to 18)</td>
<td>49% (37 to 60) 28% (18 to 39) 3% (0 to 6)</td>
</tr>
<tr>
<td>7 days</td>
<td>76% (58 to 94)</td>
<td>43% (22 to 64) 5% (0 to 14) 11% (0 to 32)</td>
<td>58% (46 to 70) 34% (22 to 46) 3% (0 to 8)</td>
</tr>
<tr>
<td>14 days</td>
<td>56% (32 to 81)</td>
<td>6% (0 to 18) 7% (0 to 19)</td>
<td>76% (52 to 94) 5% (0 to 13)</td>
</tr>
<tr>
<td>30 days</td>
<td>60% (35 to 85)</td>
<td>7% (0 to 19)</td>
<td>88% (74 to 100) 8% (0 to 19)</td>
</tr>
</tbody>
</table>

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REFERENCES