Natural history of trisomy 13

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Abstract
The poor prognosis of patients with trisomy 13 has long been accepted and has
been ascribed to brain and heart malformations. It has been suggested, however,
that the long term survival is better than was previously thought and that cardiac
surgery may be justified. This population based study reviews the incidence, antenatal
diagnosis, spectrum of survival from congenital heart disease, and mode of

There was an observed prevalence at birth of 0·049/1000 live births and an
expected prevalence, allowing for antenatal diagnosis, of 0·077. None of the
cardiac lesions found would cause early death. The median survival in this series
was four days; the longest survival was 3·5 months. The principal mode of death was
apnoea in 14 of 16 children, irrespective of the presence of a cranial abnormality. In
the light of these findings, cardiac surgery cannot be justified in patients with
trisomy 13.

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The relation of trisomy 13 to a clinical syndrome was first recognised by Patau et al in
1960.1 The fatal outcome of the children which they described, at 2 and 2·5 months of
age, was attributed to their congenital heart anomalies. Since then, several large series have
confirmed the poor prognosis of patients with trisomy 13.2–4 However, it has now been suggested
that the long term survival may be better than previously thought.5 In that study, however, as in most published reports, the
biased method of ascertainment severely limits the value of the analysis. No study has satisfac-
torily addressed the issue of why these children die. Many of the abnormalities found can now
be surgically repaired and this has been reported in children with trisomy 13.3 Even
without an operation, however, it is unlikely that the ventricular septal defects originally
described by Patau et al1 would be lethal, as there was no sign of heart failure at 1 month of
age. In light of these observations, we reviewed our experience of trisomy 13 in the Northern

Patients and methods
The Northern region of England has well
defined borders with little cross referral. All
fetal abnormalities are notified to the Northern
Regional Fetal Abnormality Survey.6 Genetic
counselling and diagnostic services are provided by the Northern Region Genetics
Service, with cytogenetic and molecular genetic
laboratories in Newcastle, and cytogenetic lab-
oratories at Middlesbrough General Hospital
and at the West Lakes laboratory in Cumbria.

Cases of trisomy 13 occurring between 1985 and 1992 were collected by reference to the
Fetal Abnormality Survey,6 which also provided necropsy data. Each case was checked
with the genetics and paediatric cardiology
databases. Details of karyotype, where per-
formed, were ascertained from records and
checked with the laboratories concerned.
Additional information was obtained from the
original notes: maternal age, child’s sex, gesta-
tion at birth or termination, age at death, and
mode of death, if born alive, were sought.

Results
There were 36 cases of Patau’s syndrome
during the eight years studied. This diagnosis
was confirmed cytogenetically in 31 patients.
In four of the remainder a necropsy showed features supportive of the diagnosis. In the
final patient the fetus was examined by one of
the authors (JB); typical features of Patau’s
syndrome were present. There was marked
variability in the incidence observed in differ-
ent years (range two to eight cases/year). Of the
36 cases, 19 were boys and 17 girls.

Of 36 pregnancies, 11 were terminated, six
ended in spontaneous miscarriage, three in
antenpartum stillbirth, and 16 infants were born
alive with trisomy 13. There were 324 139
live births in the Northern Health Region
over the same period. The observed prevalence
of Patau’s syndrome in liveborn infants in
our series is therefore 0·049/1000 live births
(1/20 258).7

Antenatal diagnosis was made in 16 cases by
amniocentesis (seven), ultrasonography
(seven), chorion villus biopsy (one), and cordoc-
entesis (one). The invasive prenatal diagnostic
techniques were performed on the basis of
maternal age in seven cases (mean 39.2 years).
Overall, the mean maternal age was 29.8 years.
In the two other cases amniocentesis was
performed after the discovery of abnormalities
on ultrasound examination. All the antenatal
diagnoses made by ultrasonography showed
fetuses with cranial abnormalities such as
holoprosencephaly or encephalocoele.

Of those detected antenatally, 11
pregnancies were terminated, three aborted
spontaneously, there was one antenpartum still-
birth, and one infant was delivered alive.
Recalculation of the prevalence taking account of
the antenatal diagnoses made is not easy. Hook
suggested in 1983 that 43% of pregnancies in which the fetus has trisomy 13
will end in spontaneous miscarriage.8 This
assumption was used by Goldstein and Nielsen
Holoprosencephaly was found in one live-born infant, meningocele in another, and encephalalocele in two further infants. All infants with these cranial defects died between the first and 22nd days of life. The terminal problem in each of these four was one of recurrent apnoea. Of the remaining 12 children, 10 died of apnoea between the first day of life and 3-5 months of age; all of these infants had normal cranial findings on ultrasound examination or at necropsy. There was no detail on the mode of death for the remaining two, but one was noted to be leaking cerebrospinal fluid from a scalp defect one week before death at home, and there had been cyanotic episodes in the first two days of life.

Three children were cyanosed before death, which was attributed to congenital heart disease. Examination of the medical and nursing notes confirms that it was associated with inadequate breathing, all children having ventricular septal defects. None of these children showed signs of heart failure.

A cytogenetic diagnosis was established in 31 infants. In 28 of these this was trisomy 13. In three infants an unbalanced translocation was identified. In each of these this was the result of a 13/14 Robertsonian translocation, the most common form of translocation in humans. One of the pregnancies in which a translocation was present resulted in a miscarriage at 9 weeks’ gestation; one was terminated after antenatal diagnosis by ultrasound examination. The third case was identified after birth. The child had ventricular and atrial septal defects and died on the third day of life.

**Discussion**

The reported prevalence of trisomy 13 varies a great deal. One of the earliest estimates by Conen and Erkman in 1966 suggested that the prevalence was 0-068/1000 live births. This estimate, however, includes several allowances for incomplete ascertainment. One of the standard texts used for reference in genetic counselling agrees with this figure, whereas another suggests the prevalence lies somewhere between 0-25 and 0-1/1000 live births. This concurs with the figure of 0-125/1000 live births suggested by Schinzel in 1979 and quoted in another commonly used text.

Goldstein and Nielsen, in their extensive review of all diagnoses of trisomy 13 made antenatally and postnatally in Denmark in a 10 year period, did not include patients with an unbalanced translocation. In calculating their figure for prevalence at birth they included stillbirths. The figure they arrived at for this was 0-034/1000 births. Making the same assumptions in our figures produces a corresponding prevalence of 0-049/1000 births. Allowing for prenatal diagnosis, using the correction suggested by Hook, Goldstein and Nielsen found an incidence of 0-053/1000 births. The corresponding figure in our group was 0-077 (Table 1).

It is likely that antenatal diagnosis is changing the spectrum of features seen in the live

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**Table 1  Prevalence of trisomy 13**

<table>
<thead>
<tr>
<th>Present study</th>
<th>Expected prevalence at birth based on live born infants (No/1000 live births)</th>
<th>Observed prevalence at 20 weeks' gestation (No/1000 pregnancies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldstein and Nielsen</td>
<td>0-049 0-077 0-107</td>
<td>0-068 0-093</td>
</tr>
</tbody>
</table>

*Based on Hook.

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**Table 2  Spectrum of congenital heart defects and cranial abnormalities in liveborn infants with trisomy 13**

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Congenital heart lesion</th>
<th>Cranial anatomy by ultrasound or at necropsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tetralogy of Fallot</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>Double outlet right ventricle</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>VSD</td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>ASD+VSD</td>
<td>Normal</td>
</tr>
<tr>
<td>5</td>
<td>VSD</td>
<td>Normal</td>
</tr>
<tr>
<td>6</td>
<td>VSD</td>
<td>Normal</td>
</tr>
<tr>
<td>7</td>
<td>VSD</td>
<td>Normal</td>
</tr>
<tr>
<td>8</td>
<td>Complete atrioventricular septal defect</td>
<td>Unknown</td>
</tr>
<tr>
<td>9</td>
<td>Unknown</td>
<td>Normal, but scalp defect leaking CSF</td>
</tr>
<tr>
<td>10</td>
<td>VSD FS</td>
<td>Normal</td>
</tr>
<tr>
<td>11</td>
<td>ASD+VSD left atrial isomerism</td>
<td>Meningocele</td>
</tr>
<tr>
<td>12</td>
<td>Unknown</td>
<td>Meningocele</td>
</tr>
<tr>
<td>13</td>
<td>VSD</td>
<td>Holoprosencephaly</td>
</tr>
<tr>
<td>14</td>
<td>ASD+VSD</td>
<td>Encephalocele</td>
</tr>
<tr>
<td>15</td>
<td>Normal heart</td>
<td>Encephalocele</td>
</tr>
<tr>
<td>16</td>
<td>Normal heart</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

VSD=ventricular septal defect; ASD=atrial septal defect; FS=pulmonary stenosis; CSF=cerebrospinal fluid.

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![Survival of trisomy 13 via ne](chart)
infant with trisomy 13. Gross cranial lesions may be less common because they are more likely to be picked up by ultrasonic screening. 13 Certainly the prevalence of cranial lesions in affected infants in this study (25%) is less than commonly quoted, 12 but our numbers are too small to show a significant difference. Fetal cardiac screening is unlikely to have an effect on the spectrum of disease seen in live infants, however, because most of the lesions noted in this series are difficult to detect even by skilled obstetric operators. 14 Only one cardiac lesion was detected antenatally by a detailed scan after earlier diagnosis by cordocentesis.

The poor prognosis for trisomy 13 is generally accepted. Magenis et al showed that 28% of the surviving newborns died in the first week, 44% within one month, and 86% within infancy. 2 Goldstein and Nielsen found a median survival of 2-5 days. 4 More recently published work has suggested a more optimistic prognosis for these children, quoting a survival rate at 12 months of 38% and a five year survival of 13%, with a mean survival of 6-6 months.Ascertainment in this study was incomplete and biased towards longevity, however, with cases being drawn from the membership of a parent support group. 5 Such selection may explain the improved prognosis observed in this series and highlights the need for population based data.

In our study all the children died by 3-5 months of age with a median survival of four days. There were only three pregnancies in which a translocation was present, however. Long term survival has been associated with this and with mosaicism for trisomy 13, 2 but has been described in free trisomy 13 in the absence of mosaicism. 3 5 15 The three pregnancies in which a translocation was present resulted either in first trimester miscarriage or in death within the first three days of life.

Cerebral and cardiovascular malformations are blamed for the poor prognosis. 1-3 12 Although the former is easy to justify, the case for the latter is less clear. In our study none of the cardiac lesions identified should have led to early death. The spectrum is similar to other published data, although slightly less severe. 16-17 It is likely that only medical treatment would be required in the first three months, if at all. If ventricular septal defects are large, cyanosis may arise during breathing or episodes of crying, but this would be transient and certainly not fatal. It has been suggested that these children have especially susceptible pulmonary vasculature and develop pulmonary hypertension, 17 but we found no evidence that this was so clinically, echocardiographically (three infants), or at necropsy (two infants).

As the heart lesions are all non-lethal, it raises the question of whether to repair them and the associated cleft lip and palate. Few would suggest such a course in the presence of any cerebral malformations, but standard texts make no such differentiation and give few reasons for early death. This is important as future children born with trisomy 13 may be less likely to have cerebral malformations because of prenatal diagnosis.

We have found that there is a high incidence of primary apnoea among infants with trisomy 13, even those with no gross cranial malformation on ultrasound or necropsy examination. Poor respiratory drive did not always manifest immediately, however. In our series no children survived longer than 3-5 months. This contrasts with the Utah study in which non-cardiac intervention was more common. 6 We had only one child in whom there was such intervention and in whom cardiac surgery was envisaged. After repair of the cleft lip and palate this child had recurrent apnoeas, which were eventually responsible for death. None of the deaths could be attributed to the cardiac lesions found.

This population based study has concentrated on the natural history of trisomy 13 in the absence of intensive intervention. It is important for paediatricians to be aware that children with trisomy 13, but without severe cranial abnormalities, still die in early infancy. Primary apnoea is the usual mode of death and parents may be warned of this with some confidence. The cardiac abnormalities are not responsible for this early death and therefore an operation is not justified. The advice, long given but difficult to rationalise, still holds good. Infants with trisomy 13, despite a few long lived survivors, die young.

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