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 death for patients with trisomy 13 in the Northern Health Region from 1985 to 1992.

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 13²⁻⁴; 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 satisfactorily 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 13.⁵ Even without an operation, however, it is unlikely that the ventricular septal defects originally described by Patau *et al*¹ 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 Health Region from 1985 to 1992.

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 laboratories 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 performed, were ascertained from records and checked with the laboratories concerned. Additional information was obtained from the original notes: maternal age, child's sex, gestation 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 different 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 antepartum 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 cordocentesis (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 encephalocele.

Of those detected antenatally, 11 pregnancies were terminated, three aborted spontaneously, there was one antepartum stillbirth, 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.⁷ This assumption was used by Goldstein and Nielsen

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Table 1 Prevalence of trisomy 13

	Observed prevalence at birth based on live born infants (No/1000 live births)	Expected prevalence at birth based on live born infants and cases detected antenatally* (No/1000 live births)	Observed prevalence at 20 weeks' gestation (No/1000 pregnancies)
Present study	0.049	0.077	0.107
Goldstein and Nielsen ⁴	0.034	0.053	

*Based on Hook.⁷

Survival of infants with trisomy 13.

when calculating prevalence figures in the Danish population.⁴ Using Hook's figure the expected prevalence of trisomy 13 from our data becomes 0.077/1000 live births (1/12 987). Assuming that our ascertainment of affected pregnancies at 18–20 weeks' gestation is complete, the prevalence is 0.107/1000 pregnancies (325 688 pregnancies at 20 weeks' gestation; one case terminated at nine weeks). Table 1 summarises these figures.

All 16 infants born alive died between one day and three and a half months after birth. The median survival was four days. The figure shows the survival of liveborn infants. Eleven had heart lesions confirmed by echocardiogram or at necropsy and three had normal hearts (there was no data on two infants). Nine infants had a ventricular septal defect, one had tetralogy of Fallot, and one an atrioventricular septal defect. One ventricular septal defect was part of a double outlet right ventricle configuration; three infants had associated atrial septal defects. Table 2 summarises the heart defects identified in liveborn infants. None of the heart lesions would be expected to be lethal in infancy or early childhood, even if left surgically untreated.

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

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

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

Holoprosencephaly was found in one live-born infant, meningocoele in another, and encephalocele 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.⁸ This estimate, however, includes several allowances for incomplete ascertainment. One of the standard texts used for reference in genetic counselling⁹ agrees with this figure, whereas another¹⁰ 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 1979¹¹ and quoted in another commonly used text.¹² 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.⁴ 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,⁷ 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

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 newborn infants 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 breathholding 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.⁵ 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 forewarned 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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