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Cytogenetic studies: an essential part of the paediatric necropsy

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SUMMARY Chromosome studies were attempted on 97% of necropsies carried out in the Department of Histopathology of the Adelaide Children's Hospital over the four-year period ending May 1981. Results were obtained from 89% of necropsies of which 7·5% had major chromosome abnormalities. The chromosome results are analysed according to the category of the necropsy and to primary cause of death. It is recommended that cytogenetic studies be performed on all stillbirths and infants dying at less than 28 days of age except in cases of isolated CNS malformation, sudden infant death syndrome (SIDS), trauma, or known single gene defects.

Chromosome studies carried out on several series of paediatric necropsies up to 1977 were summarised by Sutherland *et al*[1] and the recommendation made that such studies should form part of most paediatric necropsies. The present report documents the cytogenetic findings on all necropsies at the Adelaide Children's Hospital over an additional period of four years and makes further, more detailed, recommendations concerning the application of chromosome studies at the paediatric necropsy.

Material and methods

All routine paediatric necropsies at the Adelaide Children's Hospital were studied. During the period of study the annual necropsy rate fluctuated between 75% and 80%, the majority of those not coming to necropsy having died from long standing illnesses such as cystic fibrosis, thalassaemia and malignant disease. In addition some stillbirths and neonatal deaths occurring outside the Hospital were referred for necropsy and all sudden infant deaths in South Australia were examined under the authority of the Coroner. Such studies were carried out for a six-year period ending May 1981; the results of the first two years have been published,[1] hence this report covers the last four years of the period.

Methods of chromosome study have been previously recorded.[1] Perinatal deaths are defined as stillbirths of more than 28 weeks gestation and liveborn infants who lived for less than one week, regardless of gestation. The perinatal deaths were further subdivided into macerated stillbirths, non-macerated stillbirths and early neonatal deaths. Older neonate refers to a baby dying between 8 and 28 days after birth, infant to a death occurring between 29 and 365 days after birth and child to a death occurring on or after the 366th day of life.

Results

The chromosome results are shown by category of necropsy in Table 1. Chromosome results were obtained for 89% of necropsies, the major area of failure being macerated stillbirths where results were obtained from only 54% of those studied. Despite their high failure rate, macerated stillbirths are considered worthy of study since they yielded the second highest proportion of chromosome anomalies. Therapeutic abortions of course had the highest yield since in many cases these were performed as the result of a prenatal diagnosis of a chromosome abnormality.

The chromosome findings according to cause of death are shown in Table 2 for the whole series excluding the therapeutic abortions and spontaneous abortions of less than 20 wk gestation. The chromosome abnormalities found in the SIDS were a 46,XY/47,XYY mosaic and a t(X;5) in a male known to have this abnormality prior to death, having been investigated for severe hypospadias.

The chromosome abnormalities detected are shown in Table 3. The majority of these are typical of those found at prenatal diagnosis (mainly autosomal trisomies) or of those dying in childhood—for example, Down's syndrome. There was one case of the very rare 45,X male found in a babe dying on the

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Table 1 *Chromosome results according to category of necropsy*

Category	*Total*	*Chromosome studies attempted*	*Successful*	*Normal karyotype*		*Abnormal karyotype*	
				Male	*Female*	*No*	*%*
Therapeutic abortion	31	29	28	6	9	13	46
Spontaneous abortion (less than 20 wk)	7	7	3	3	0	0	0
Spontaneous abortion (more than 20 wk)	4	4	3	3	0	0	0
Macerated stillbirth	51	48	26	12	9	5	19
Non-macerated stillbirth	21	20	19	7	10	2	11
Early neonatal death	38	38	38	20	13	5	13
Later neonatal death	25	25	24	15	9	0	0
Older than 28 days	210	208	199	107	87	5	2·5
Older than 1 yr	151	143	141	84	52	5	3·5
Total	538	522	481	257	189	35	7·5

Table 2 *Chromosome results according to primary cause of death (therapeutic abortions and abortions of less than 20 wk gestation excluded)*

Cause of death	*Total*	*Chromosome studies attempted*	*Successful*	*Normal karyotype*		*Abnormal karyotype*	
				Male	*Female*	*No*	*%*
Macerated without malformation	41	37	18	7	9	2	11
Macerated with malformation	3	3	2	0	0	2	(100)
Prematurity associated disease	3	3	3	2	1	0	0
Primary CNS malformations	41	41	38	17	21	0	0
Severe congenital malformations	49	49	47	14	9	23	49
Congenital heart malformation	56	56	56	29	25	2	3·6
Primary anoxia	23	22	19	11	7	1	5·3
Infection	27	27	25	14	11	0	0
SIDS	142	141	135	81	52	2	1·5
Leukaemia	15	15	15	9	6	0	0
Other malignancy	18	18	18	11	7	0	0
Trauma	54	45	44	28	16	0	0
Mendelian disorders	21	21	20	14	6	0	0
Miscellaneous	37	37	37	18	18	0	0
Total	530	575	477	255	188	32	6·7

Table 3 *Chromosome abnormalities detected*

		Chromosome abnormality	*No*
(a)	Amongst the therapeutic abortions	47,XX or XY,+21	6
		46,XX,rob(13;14)mat,+21	1
		triploid	2
		47,XX,+mar	1
		47,XY,+13	1
		47,XX,+del(22q)	1
		46,XX,del(5p)	1
(b)	Amongst the others	(i) *Sex chromosome anomalies*	
		46,XY (female)	1
		45,X (male)	1
		45,X	1
		46,XY/47,XYY	1
		(ii) *Autosomal anomalies*	
		47,XX or XY,+21	5
		46,XY/47,XY,+21	1
		46,XX or XY,+18	4
		47,XY,+13	1
		46,XX/47,XX,+2	1
		45,XY,rob(14q21q)	1
		46,Y,t(X;5)(q13;p15)	1
		46,XX,14q+	1
		46,XX,del(5p)	1
		46,XX,del(6p)	1
		46,XY,del(4q)	1

second day of life from cardiac failure due to a hypoplastic left heart. His external genitals were normal as was testicular histology. The mosaic trisomy 2 had 17/27 cells examined showing trisomy 2. This was one of macerated twins stillborn at 37 wk gestation; there was a single placenta and chromosome studies were from amnion. The main necropsy finding was of intrauterine hypoxia and there was evidence of growth disturbance at the costochondral junction. The findings in the second twin were similar except that the karyotype was normal female. The infant with del(5p) was an intrapartum death and apart from borderline microcephaly no unusual findings were made at necropsy.

Discussion

The incidence and type of chromosome abnormalities detected in this series is similar to other published series.[1-3] The repeated finding of mosaic trisomy 2 is of interest since there is some doubt as to whether this is a true chromosome abnormality or an in vitro chromosome change which is particularly likely to occur when amnion is used for chromosome study. In the present series the finding of mosaic trisomy 2 in one of probably monozygous twins, with the other having a normal karyotype, suggests

Table 4 *Results of chromosome studies on unselected paediatric necropsies**

Status	*No studied*	*No abnormal*	*% abnormal*
Macerated stillbirth	138	18	13
Non-macerated stillbirth	359	15	4·2
Early neonatal death	862	46	5·3
Late neonatal death	110	5	4·5
Infant	402	19	4·7
Child	235	12	5·1

*Taken from references 1–3 and the present series.

that this finding is most likely to be due to in vitro change.

In Table 4 the results of this series of paediatric necropsies have been added to those summarised previously.[1] In the macerated stillbirth group the incidence of chromosome abnormality is around 13% and in all other groups it is in the region of 4–5%. Apart from occasional sex chromosome abnormalities and balanced translocations, virtually all the chromosome abnormalities in infants and children had been recognised prior to necropsy.

The value of chromosome results, even the normal results, cannot be over-emphasised. Genetic counselling should be offered to all couples who lose a child in the perinatal period and since the question of prenatal diagnosis arises in most genetic counselling situations knowledge of the chromosome results of the dead child are particularly valuable. In the present series the finding of del(5p) in a stillbirth, potentially a case of the cri du chat syndrome, was of immense help to the parents. It provided them with a reason for the death, alleviated some of their grief with the knowledge that had the child survived it would have been severely handicapped, and after they themselves had been shown to have normal karyotypes, provided positive reassurance that the recurrence risk was very small.

There are several causes of death in which chromosome abnormalities are no more common than amongst unselected liveborn children. These include deaths due to primary CNS malformation (mainly anencephaly and spina bifida), SIDS, trauma and known single gene defects. Since these diagnostic categories will usually be known by the time of the necropsy, and since there are very few unknown chromosome abnormalities detected in babies who have lived for more than one month, the following guidelines are suggested for the use of chromosome studies at the paediatric necropsy. Studies should be done on all infants dying at less than 28 days of age and on all stillbirths, except in cases of isolated CNS malformation, SIDS, trauma or known single gene defects. It is important that these exceptions are properly identified and not interpreted too loosely. For example, it is important to ensure that a CNS malformation is an isolated defect and not just one of many malformations present as occurred in one case of trisomy 18 in the present series where the most obvious feature prior to detailed examination of the neonate was spina bifida. Obviously infants older than 28 days in whom there are indications for chromosome studies should be karyotyped if this has not been done prior to necropsy.

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