Journal of Medical Genetics (1976). **13**, 9–16.

Congenital malformations of the central nervous system in spontaneous abortions

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Summary. A study of 2620 pregnancies ending in spontaneous abortion revealed a CNS defect in 3.6% of embryos and fetuses, and 3% of all complete conceptuses. The type of malformation observed varied with the gestational age at expulsion, encephaloceles being predominant in earlier specimens, while more typical anencephalus and spina bifida were more common among later abortions.

Chromosome abnormalities were found in 40% of abortuses with CNS defects, but were almost entirely confined to those which were still at the embryonic stage of development. 53% of the latter were chromosomally abnormal, which is the same as the proportion found among embryos without a CNS malformation.

Using published life-tables of recognized pregnancies it was estimated that the prevalence of anencephalus, spina bifida, or related malformation (other than hydrocephalus), without a chromosome anomaly, is 5.3 per thousand conceptuses at the beginning of the eighth week of gestation. By comparing this with the prevalence in total births, it was further estimated that only 24% of these are born alive, with 54% aborting spontaneously and 22% being stillborn.

Most investigations into the prevalence and causes of central nervous system malformations have considered only livebirths and registered stillbirths. It has long been suspected that affected conceptuses are aborted disproportionately often, though we do not yet know what proportion is lost in this way. Moreover, it is not known how the aborted conceptuses compare with those that survive until birth from a pathological or aetiological point of view. Singh and Carr (1967) examined 168 spontaneously aborted embryos and fetuses and found two with a meningocele and one with an encephalocele (18 per thousand). They also found one abortus with an enlarged, eccentric spinal cord. Nishimura (1970), in Japan, found 49 CNS defects in 3715 induced abortions (13 per thousand), including 21 cases of exencephalus or myeloschisis (5.7 per thousand).

Data on these issues may be useful for several reasons. First, as prenatal diagnosis of high-risk pregnancies is now becoming increasingly common, knowledge of the prognostic significance of such a diagnosis will increase the accuracy of genetic counselling. Second, all the important epidemiological studies in this field have been carried out on a selected group of affected infants, namely those reaching a potentially viable stage of development (for review, see Leck, 1974), and it is possible that associations have been missed. Third, these issues bear indirectly on the suggestion that much of the geographical, and possibly other, variation in birth prevalence may reflect variation between mothers, or even between pregnancies, in their tendency to abort affected conceptuses (Roberts and Lloyd, 1973).

Received 21 January 1975.

Methods

With the co-operation of the medical and nursing staffs of gynaecological units in and around London, women who had a spontaneous abortion between September 1971 and April 1974 were interviewed regardless of the presumptive cause. In almost all cases the products of conception were collected for investigation, though often only curettings of these were available. When the conceptus was more than 30 mm in length (ie. a fetus), a macroscopical examination and dissection were carried out. Smaller specimens were studied under a binocular low-power microscope and kept in fixative for

more detailed study later. Unless the specimen was extremely macerated, pieces of amnion, gonad, or other fetal tissue were taken for culture from explants, and chromosome preparations were made. According to the date of their last menstrual period, a few specimens were technically beyond the gestational age limit for abortions (27 weeks), but were included because they were extremely small for their dates.

Results

Prevalence

The 2620 pregnancies (2582 singleton and 38 twin) which were studied included 995 complete, organized fetuses in which any gross malformation present could have been detected. 36 (3.6%) were found to have a lesion of the CNS (Table I). However, a further 221 specimens were intact empty sacs or severely disorganized embryos, making a total of 1216 specimens which could be examined. The crude prevalence of these CNS defects is therefore estimated as 36/1216, or 3%, among testable abortuses in the London area in the early 1970's.

TABLE I

OUTCOME OF 2620 SPONTANEOUS ABORTIONS

Total pregnancies studied	2620
Twin pregnancies	+38
Total conceptuses	2658
No recognizable fetus or sac	−810
Incomplete fetus or ruptured sac	−632
Complete fetus or intact sac	1216
Disorganized embryo or empty sac	−221
Complete, organized fetus	995
With CNS malformation	−36
With other malformation	−38
Apparently normal fetus	921

This will be compared with the prevalence at birth in a subsequent section.

Types of malformation

A wide range of CNS malformations was observed, often in association with other anomalies, notably cleft-palate (Table II and Appendix). Four affected specimens had multiple anomalies, in one case those of Meckel's syndrome (case 16). Another (case 3) was a monozygotic twin, whose cotwin had identical malformations with the exception of the CNS defect—a myelomeningocele.

The type of CNS malformation appeared to vary with the gestational age at expulsion (Table III). Encephaloceles predominated among the younger abortuses. These were mostly small in relation to the size of the head, and in many cases it was difficult or impossible to decide whether the brain protruded through the fissum, or whether the malformation was strictly a cranial meningocele. All such lesions have been described as encephaloceles. Typical anencephalus was seen only in older abortuses, while exencephalus was found in those of intermediate age. One specimen with anencephalus and one with a large encephalocele had reputed ages of 29 and 28 weeks, respectively, but they, like a few others, were counted as abortions because of their size (see methods section).

Chromosomes

The chromosome constitution was determined for 25 of the 36 affected abortuses, and 10 (40%) were found to have a chromosome abnormality (Table IV). The corresponding figure for 544 karyotyped embryos and fetuses without a CNS lesion was 13%.

TABLE II

MALFORMATION IN FETUSES WITH A CNS DEFECT

CNS Malformation	No Other Malformation	Malformation of Other System	Total
Spina bifida (sb)	2	1 cleft palate 2 MSA*	5
Encephalocele	11	4 cleft palate 1 MSA* 1 talipes	17
Encephalocele + sb	1	0	1
Exencephalus	5	0	5
Exencephalus + sb	0	1 pulmonary hypoplasia	1
Exencephalus acrania + sb	1	0	1
Anencephalus	1	0	1
Anencephalus with cervical retroflexion + sb	0	1 bilat. flexion deformity of the fingers	1
Craniorachischisis	2	0	2
Hydrocephalus	0	1 MSA*	1
Cyclopia	1	0	1
Total	24	12	36

* Multi-system anomalies. Full details in appendix.

TABLE III

TIME OF EXPULSION OF FETUSES AND EMBRYOS WITH CNS DEFECTS

CNS Defect	Gestational Age (wk)						Total
	< 12	12–15	16–19	20–23	24–27	> 27	
Spina bifida	1	1	1	1	1	0	5
Encephalocele	5	9	3	0	0	1	18
Exencephalus	1	1	2	1	1	0	6
Exencephalus acrania	0	1	0	0	0	0	1
Anencephalus	0	0	0	0	1	1	2
Craniorachischisis	0	1	0	0	1	0	2
Hydrocephalus	0	0	1	0	0	0	1
Cyclopia	1	0	0	0	0	0	1
Total	8	13	7	2	4	2	36

TABLE IV

CHROMOSOME CONSTITUTION OF 995 COMPLETE FETUSES AND EMBRYOS

Fetus	Karyotype			Total
	Unknown	Normal	Abnormal	
With CNS defect	11	15	10	36
Without CNS defect	415	480	64	959
Total	426	494	74	995

However, as the proportion of abortuses that have chromosomal aberrations is known to decrease sharply with increasing gestational age (Alberman and Creasy, 1975; Boué and Boué, 1969) a crude comparison, without allowance for the differing gestational age structure of the two sub-groups, would not be justified.

Of the 12 (of 35) CNS-defect specimens that exceeded 30 mm in crown-rump length, only one was shown to be chromosomally abnormal—a hydrocephalic triploid (69,XXX). Of the 12, 4 could not be examined chromosomally—spina bifida (2), exencephalus (1), anencephalus (1). The remaining 7 were chromosomally normal—encephalocele (3), exencephalus (2), anencephalus (1), and craniorachischisis (1). The chromosome abnormality rate is thus 1 in 8 among the large affected specimens, not significantly different from the rate of 4% (17 out of 454) among specimens of the same length without a CNS defect.

Chromosome anomalies were much more common in specimens that were not more than 30 mm long, whether maldeveloped or not (Table V). 53% of all those that could be examined were chromosomally abnormal, irrespective of whether they possessed a CNS defect or not. The affected subgroup included cases of sex chromosome monosomy, autosomal trisomy, triploidy and, in one specimen, an XXY sex chromosome complement with an additional F-like autosome (48,XXY,+F). Autosomal trisomy accounted for 39% of the aberrations in the morphologically normal embryos, but only 2 out of 9 (22%) in those with a CNS defect. The former group included trisomies of the C, D, E, and G group autosomes, the latter two being the most common. Both the trisomic embryos with a CNS defect had an extra member of the D group, and also cleft palate.

Sex

Of the fetuses which were past the embryonic stage of development (taken as those greater than 30 mm long) 5 were female, 5 were male, and 2 were of uncertain sex (Table VI). Those with anencephalus, craniorachischisis, or spina bifida

TABLE V

CHROMOSOME CONSTITUTION OF 107 EMBRYOS ≤ 30 mm CR

CNS defect	Chromosome Constitution						Total
	Normal	45,X	D Trisomy	Other Trisomy	Triploid	Other	
Encephalocele	5	4	2	0	0	1	12
Exencephalus	3	0	0	0	0	0	3
Exencephalus acrania	0	0	0	0	1	0	1
Spina bifida	0	0	0	0	1	0	1
All CNS defects	8	4	2	0	2	1	17
No CNS defect	42	16	2	16	7	7	90

TAVLE VI

SEX (MORPHOLOGICAL AND/OR CHROMOSOMAL) OF FETUSES, GREATER THAN 30 mm CROWN-RUMP, WITH A CNS MALFORMATION

Malformation	Male	Female	Unknown	Total
Spina bifida	0	1	1	2
Anencephalus	0	2	0	2
Craniorachischisis	0	1	0	1
Hydrocephalus	0	1	0	1
Exencephalus	2	0	1	3
Encephalocele	3	0	0	3
Total	5	5	2	12

cystica included 4 females and no male, and the hydrocephalic was anatomically female. All 5 specimens with exencephalus and encephaloceles were male.

Family history

The obstetric histories of women who miscarried a conceptus with a CNS defect are summarized in Table VII. Two fathers had a mentally subnormal niece or nephew, one of whom was hemiplegic. The cousin of one father had a cleft palate, another father was the child of two deaf and dumb parents. The maternal aunt of one conceptus had a congenital heart defect. Only this abortus, of the five with a family history of congenital malformation, had a known chromosome abnormality (45,X).

There was 1 anencephalic stillbirth among 35 previous births to the mothers of affected fetuses. As these births were derived from a total of 46 recognized pregnancies, the previous abortion rate is at least 11/46, or 24%.

Estimate of prevalence

Before the prevalence of CNS malformations in abortuses can be estimated and compared with the prevalence at birth, it is necessary to consider a number of points.

In many instances the products of miscarriage collected after hospital admission do not include an embryo or fetus. In some cases this is because the conceptus did not develop a recognizable embryo, but more often because the membranes have ruptured and the contents have been expelled. Obviously, when a ruptured sac, an incomplete fetus, or placental or maternal tissue only was received, diagnosis of malformation was impossible. Calculation of the proportion of CNS defects among complete fetuses only might well have overestimated their frequency in all pregnancies, because a number of conceptions consisted of an empty sac only, with no embryo, or of a disorganized mass of embryonic tissue. The frequency of CNS defects in pregnancies has, therefore, been calculated as a fraction of all 'complete' specimens, a complete specimen being defined as an intact empty sac, or an entire embryo or fetus, with or without its sac. This probably underestimated the true number of empty sacs, but the results could not be based on intact sacs alone, as this would have excluded almost all larger fetuses.

Another problem concerns the gestational age distribution of the sample. In any abortion series there is always a deficit of specimens lost at the earliest stages of pregnancy. As lesions of the CNS were found more frequently in such early specimens, an attempt was made to correct for this sampling bias by constructing a life-table. This would also allow a comparison of the figures for abortions with those for still- and livebirths. The basis of the life-table was derived from the Kauai pregnancy study (KPS) carried out on a Hawaiian island between 1953 and 1956 (French and Bierman, 1962). The island appears to have had extremely good antenatal facilities, and the stillbirth rate (less than 13 per thousand births) compares well with recent rates for South-East England (11 per thousand) and Greater London (12 per thousand), (Registrar General's figures for 1971). The KPS findings have been corroborated, at least for the period of gestation under consideration, by studies in Belfast in 1957 (Stevenson and Warnock, 1959) and in New York in 1958 (Shapiro, Jones, and Densen, 1962).

Column two of Table VIII includes all complete

TABLE VII

OBSTETRIC HISTORIES OF 36 MOTHERS OF ABORTUSES WHICH HAVE A CNS DEFECT

Karyotype of Current Abortus	No. of Mothers	Mothers with No Previous Pregnancies	No. of Any Previous Pregnancies	No. of Any Previous Spontaneous Abortions	No. of Previous Stillbirths	No. of Previous Livebirths
Not known	11	5	14	5	1 anencephalic	8
Normal	15	8	13	4	0	9
Abnormal	10	2	19	2	0	17
Total	36	15	46	11	1	34

TABLE VIII

ESTIMATED MORTALITY TABLE OF COHORT OF CONCEPTUSES COUNTED (NOTIONALLY) AT WEEK 8; ALL CAUSES (COL. 5) AND ASB-ASSOCIATED CAUSES (COL. 6)*

1	2	3	4	5	6	7
Mode of Spontaneous Termination of Pregnancy, or Expulsion of Conceptus	No. of Complete Specimens Studies	Observed No. With ASB	Estimated ASB Prevalence among Terminations of Indicated Category (per 1000)	Estimated No. of Conceptuses (of a cohort of 1000 counted at week 8) Expelled in Way Indicated	Estimated No. of Conceptuses (of cohort) Expelled with ASB in Way Indicated	Estimated % of All ASB in Cohort Expelled in Way Indicated
	n	n_a	$1000.n_a/n$	N	$N_a = N.n_a/n$	$100.N_a/5.29$
Aborted at:						
8–11 wk	232	5	21.6	69.90	1.51	28.6%
12–15 wk	316	7	22.2	41.65	0.92	17.4%
16–19 wk	247	5	20.2	11.83	0.24	4.5%
20–23 wk	239	2	8.4	154.80 → 143.54	4.01 → 2.83	75.8% → 53.5%
24–27 wk	109	4	36.7	7.42	0.06	1.9%
Stillborn:				2.74	0.10	
(>27 wk)	5741	604	105.2	11.26	1.18	22.3%
Liveborn:	403 725	605	1.5	855.20 → 866.46	1.28 → 2.46	24.2% → 46.5%
				1000.00	5.29	100.0%

* Data for outcome of pregnancy (col. 5) from French and Bierman (1962). ASB data for live and stillbirths from Carter and Evans (1973) and for spontaneous abortions from present study.

abortuses, as defined above, with a known gestational age between 8 and 27 weeks, inclusive, and a series of live- and stillbirths in Greater London reported by Carter and Evans (1973). Column three shows the number of these with a CNS defect. Only those abortuses with an ASB-type malformation (anencephalus, craniorachischisis, exencephalus, encephalocele, or spina bifida cystica), but no demonstrated chromosome anomaly, have been included, as only these were felt to be comparable with the classification of malformations used for births.

The proportion of affected conceptuses that is lost during each 4-week period of gestation was estimated, in each case, from the proportion with a malformation in the present study among the pregnancies at risk, as given by the life-table.

The calculations show that the prevalence of these malformations remains fairly constant among earlier fetal deaths, decreases towards the end of the previable period, and then increases to a maximum in late abortions and stillbirths. The overall rate among spontaneous abortions is estimated to be about 20 per thousand. This is one-fifth of that among stillbirths (105 per thousand), but is more than 13 times the rate among livebirths in the same area (1.5 per thousand) (Carter and Evans, 1973). The figures indicate that at the beginning of the eighth week of gestation, just over 5 per cent of all conceptuses have a recognizable malformation of the ASB type as defined above, but that 75% of these fail to be born alive, with more than two-thirds of this mortality occurring as spontaneous abortion (Tables VIII and IX). About 85% of term ASB

TABLE IX

ESTIMATED PREVALENCE OF ASB MALFORMATIONS AT DIFFERENT STAGES OF GESTATION FOR COHORT COUNTED (NOTIONALLY) AT WEEK 8*

Stage of Gestation (beginning of week)	Estimated No. of Surviving Pregnancies of Cohort Counted at Week 8	Estimated No. of Conceptuses with ASB in Cohort	Estimated Prevalence of ASB in Surviving Pregnancies of Cohort (per 1000)
8	1000.00	5.29	5.29
12	930.10	3.78	4.06
16	888.45	2.86	3.22
20	876.62	2.62	2.99
24	868.83	2.56	2.95
27	864.73	2.46	2.84

* Same sources as Table VIII.

infants are recorded as stillborn, though the true proportion must be lower, as many liveborn, malformed infants which live only a few minutes or hours are registered as stillbirths for humanitarian reasons.

Discussion

The results of this study show that the most common group of malformations in abortuses is a type apparently related to anencephalus and spina bifida. These latter form the most common category of malformation found at birth, in the U.K.

The gestationally older fetal deaths (those occurring from about the 20th week onwards) exhibit very similar lesions to those seen in births, while encephaloceles predominate among those expelled earlier in pregnancy. The small embryos will require microscopical examination of sections for accurate diagnosis of their anomalies, but this is

TABLE X

RELATION BETWEEN TYPE OF MALFORMATION, SIZE OF EMBRYO OR FETUS, AND CHROMOSOME CONSTITUTION

Malformation	Crown-rump Length (mm)				
	≤30	31–60	61–90	91–120	>120
Spina bifida	2 unknown 1 triploid	1 unknown			1 unknown
Encephalocele	3 unknown 5 normal 4 XO 2 D trisomy 1 other			2 normal	1 normal
Exencephalus	3 normal	1 unknown 1 normal			1 normal
Exencephalus acrania Anencephalus	1 triploid		1 unknown 1 normal		
Craniorachischisis Hydrocephalus	1 unknown		1 normal 1 triploid		

not necessary for the purposes of the present account, concerned as it is with the prevalence of CNS defects in general.

The qualitative difference between the types of CNS malformation associated with death in the earlier stages of pregnancy and those found in conceptuses which survive longer poses an important question: are these defects of different aetiology, or is one the forerunner of the others, seen at an earlier stage of development? In this connexion, the frequency of chromosome anomalies in malformed conceptuses during different periods of gestation is important.

The CNS anomalies found at birth are not generally considered to be associated with chromosome aberrations, but there is little information available. A study of 6 families with affected children revealed 1 father with a deleted chromosome 15 and another with an apparent short arm interchange between two D group chromosomes (Spellman, 1966). A mother with a mixoploid C chromosome trisomy (Stolte, Evers, and Bankenborg, 1964) and a father with a balanced translocation involving two D group chromosomes (de Grouchy *et al*, 1964) have also been reported. In the infants themselves, Machin and Crolla (1974) found one anencephalic with a balanced translocation among 50 karyotyped perinatal deaths with ASB or hydrocephalus. An unbalanced translocation producing partial 2 trisomy (Lee *et al*, 1964) and an anencephalic male with XX sex chromosomes (Arias-Bernal and Jones, 1967) have been described. Trisomy D, trisomy 18, and triploidy are often associated with various CNS defects (Warkany, 1971; Niebuhr *et al*, 1972; Batts *et al*, 1972) but not usually those of the ASB type.

Of the larger affected abortuses in the present series, only 9 were karyotyped and 1 was found to be chromosomally abnormal, but this specimen did not have an ASB malformation. Thus, in this respect also, the older abortuses may resemble the perinatal deaths. By contrast, 53% of the smaller affected abortuses (embryos 30 mm or less in length) had a chromosome aberration. However, these aberrations are found in this proportion of all abortuses of this size, so that it is difficult to decide whether the malformation was independent of, or secondary to, the chromosomal condition. The fact that D trisomy was the only trisomy found is interesting, because of the association between this condition and some CNS defects, as mentioned above. It seems possible that some chromosome conditions (possibly those involving D group chromosomes) may produce minor CNS lesions which do not develop into ASB malformations, while in other instances defects which do not produce such malformations coincide, by chance, with chromosome anomalies. Because both conditions have very high mortalities in early pregnancy, few survive until the perinatal period. If some embryos with abnormal chromosomes do have a true ASB type lesion, which is not a result of their karyotype, the prenatal mortality is higher than the estimate given.

It is evident that a family of malformations of the central nervous system, which includes anencephalus and spina bifida, is relatively common during the early stages of pregnancy, and that within this group, encephaloceles and exencephalus predominate. The former are often associated with chromosomal abnormalities, to which they might be secondary, though they are found in conditions such as sex chromosome monosomy, with which they are not usually associated at full term, and karyotypically normal conceptuses. Exencephalus, however, does not appear to have any links with chromosomal conditions. These two anomalies have the greatest prenatal loss, so that in the later stages

of pregnancy anencephalus and spina bifida are the most numerous anomalies within the group (Table IX). The genetic and environmental factors producing these defects must be very complex and the group of malformations, and probably the subgroups within it, are probably heterogeneous in relation to them. It is possible that more can be learned of these aetiological factors by studying the malformation early in gestation, closer to the time of their appearance. Certainly it would be interesting to compare the loss through abortion in London with that from an area, such as South Wales or Ireland, where the prevalence at birth is higher.

The authors are indebted to Dr J. H. Renwick for his valuable help with the manuscript and Dr C. O. Carter and Mrs K. Evans for allowing us access to their data. We also wish to thank the many gynaecologists who allowed us to study the products of conception of their patients with spontaneous abortion; Dr C. L. Berry and Dr G. A. Machin for examining a number of the specimens; Miss M. H. Elliott for interviewing many of the patients and much other assistance; and Mr J. A. Crolla and Mrs A. R. Grant for technical assistance.

The study was supported by grants from the Medical Research Council, Schering Chemicals Ltd., and the Spastics Society.

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APPENDIX

Details of fetuses with CNS malformations

No.	Gestational Age (wk)	Crown-rump Length (mm)	Anatomical Sex (Fetuses > 30 mm)	Karyotype	Description
1	24	150	M	46,XY	Exencephalus, spina bifida occulta of L3; pulmonary hypoplasia
2	17	60	?	NK	Exencephalus
3	18	47	NK	NK	One of presumably monozygotic twins with monoamniotic placentation and vellamentously inserted, forked cord; sacral meningomyelocele; large exomphalos (liver and small intestine) in proximal part of cord; anal atresia; no external genitalia

APPENDIX—*continued*

Details of fetuses with CNS malformations—continued

No.	Gestational Age (wk)	Crown-rump Length (mm)	Anatomical Sex (Fetuses >30 mm)	Karyotype	Description
4	29	80	F	NK	Anencephalus with cervical retroflexion; sacral meningocele; bilateral flexion deformity of 3rd finger
5	24	75	F	46,XX	Anencephalus
6	21	30		NK	Spina bifida cystica
7	24	67	F	46,XX	Craniorachischisis
8	12	110	M	46,XY	Occipital encephalocele
9	13	23		46,XY	Occipital encephalocele
10	28	160	M	46,XY	Occipital encephalocele; bilateral ulnar polydactyly (6 digits); large cystic kidneys; anomalous external genitalia (Meckel's syndrome)
11	11	19		47,XX,+D	Parieto-occipital encephalocele; bilateral cleft lip
12	12	19		46,XX	Occipital encephalocele; bilateral cleft lip
13	11	15		NK	Frontal encephalocele
14	19	110	M	46,XY	Fronto-parietal encephalocele; prominent eyes; left talipes equinovarus
15	7	20		NK	Thoracic spina bifida cystica
16	25	150	F	NK	Severe left scoliosis of thoracic and lumbar regions of vertebral column, greatly reducing left hemithorax; ectopia cordis; exomphalos (liver and jejunum); right pulmonary aplasia; enlarged right ovary; reduction deformity of toes, probably left talipes; fleshy appendage on sole of right foot; Meckel's diverticulum; single umbilical artery; lumbosacral meningocele
17	22	19		46,XX	Exencephalus
18	13	20		45,X	Parieto-occipital encephalocele
19	11	20		NK	Parietal encephalocele; spina bifida cystica
20	19	17		45,X	Frontal encephalocele
21	13	7		69,XXY	Exencephalus acrania; spina bifida cystica
22	10	22		NK	Cyclopia
23	10	29		46,XX	Frontal encephalocele
24	14	29		46,XY	Occipital encephalocele
25	14	30		46,XY	Exencephalus
26	18	43	M	46,XY	Exencephalus
27	11	16		48,XXY,+F	Encephalocele
28	15	30		NK	Craniorachischisis
29	15	22		69,XXY	Lumbar spina bifida cystica; cleft palate
30	13	20		45,X	Parietal encephalocele
31	13	12		47,XX,+D	Frontal encephalocele; cleft lip
32	16	85	F	69,XXX	Hydrocephalus; pulmonary hypoplasia; renal agenesis; left talipes equinovarus
33	12	15		45,X	Parietal encephalocele
34	17	22		NK	Encephalocele; bilateral cleft lip
35	12	16		46,XX	Frontal encephalocele
36	9	28		46,XYq+	Exencephalus

NK = not known.