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Choroid plexus cysts and chromosomal defects

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Abstract. During a 4-year period, 83 pregnant women with fetal choroid plexus cysts were investigated in our unit. Abnormal karyotypes were found in 20 fetuses, including trisomy 18 ($n=16$), trisomy 13 ($n=1$), triploidy ($n=1$) and translocation Down's syndrome ($n=2$). All fetuses with chromosomal defects had structural malformations in addition to the choroid plexus cysts.

The ultrasound diagnosis of fetal choroid plexus cysts was first reported in 1984; in all five fetuses the cysts had resolved spontaneously by 23 weeks and it was suggested that the cysts were of no pathological significance (Chudleigh et al, 1986). However, it was subsequently noted that if the cysts are associated with other malformations, such as cerebral ventriculomegaly, congenital diaphragmatic hernia, exomphalos or obstructive uropathy, they may indicate the presence of an underlying trisomy 18 (Nicolaides, 1986). A series of reports have since reinforced this possible association between choroid plexus cysts and chromosomal abnormalities (Ricketts et al, 1987; Furness, 1987; Chitkara et al, 1988; Ostlere et al, 1989; Khouzam & Hooker, 1989; Gabrielli et al, 1989). This study reports the findings in 83 fetuses with choroid plexus cysts that were examined in our centre.

Patients and methods

In a 4-year period (September 1985–November 1989) we investigated 83 cases of fetal choroid plexus cysts. The indication for referral to our centre included the detection of choroid plexus cysts ($n=39$) or other fetal malformations ($n=27$) at the routine ultrasound examination in the referring hospitals, pre-natal diagnosis of haemophilia A or epidermolysis bullosa ($n=2$), raised maternal serum alpha feto-protein ($n=4$), oligohydramnios ($n=3$) and fetal karyotyping for maternal age or low maternal alpha feto-protein ($n=8$).

In our centre, a detailed ultrasound examination was performed for fetal biometry and the exclusion or diagnosis of fetal malformations. The choroid plexuses were examined in the standard biparietal diameter view, but care was taken to examine both hemispheres and avoid the mistaken diagnosis of unilateral lesions. The best view to determine bilaterality is one midway between the transaxial and coronal sections (Fig. 1).

Subsequently, parents were counselled as to the possible association with chromosomal defects and it was explained that in the presence of additional malformations the risk was thought to be high whereas if the cysts were isolated the risk was likely to be extremely small. The parents were also told that the procedure related risks of fetal loss from the various invasive techniques for karyotying was approximately 1%.

In 46 of the cases, the parents requested fetal karyotyping and cordocentesis ($n=43$) or amniocentesis ($n=3$) was performed as an outpatient procedure. In all cases where karyotyping was not undertaken, and in those where the karyotype was normal, patients were rescanned at 4-weekly intervals until resolution of the cysts was observed. Subsequent management of the pregnancies was undertaken by the referring obstetricians, who also provided details on outcome.

Results

In 82 of the 83 cases the choroid plexus cysts were bilateral. The size of the cysts varied considerably, ranging from 3–21 mm in maximum diameter. No relationship was found between the size or shape of the cysts and other findings.

Additional malformations were found in 34 fetuses (Table I) and in all cases karyotyping was undertaken. In 20 (59%) of these fetuses there were chromosomal defects including trisomy 18 ($n=16$), trisomy 13 ($n=1$), triploidy ($n=1$) and translocation Down's syndrome ($n=2$). The predominant malformations in the chromosomally abnormal group were exomphalos ($n=7$), congenital diaphragmatic hernia ($n=4$), congenital heart disease ($n=5$), oesophageal atresia ($n=2$) and polyhydramnios ($n=3$). Furthermore, 16 of the 20 fetuses were severely growth retarded. The characteristic facial and digital defects of trisomy 18 and 13 were found in 14 cases. Both infants with translocation Down's syndrome had nuchal skin oedema. In contrast, in the chromosomally normal group the predominant associated malformations were renal.

In the chromosomally abnormal group, 18 of the 20 pregnancies were electively terminated and two resulted in an intrauterine or neonatal death. In the chromosomally normal group, six infants were liveborn and of

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Table 1. Ultrasonic findings, karyotype and outcome of 34 fetuses with choroid plexus cysts and additional malformations

Case number	Gestational age (weeks)	Karyotype	Biometry	Other malformations	Outcome (weeks)
1	15	47,XY,+18	SGA	Exomphalos, strawberry head, atrioventriculoseptal defect	TOP (19)
2	17	47,XX,+18	SGA	Exomphalos, strawberry head, digital defects, facial cleft, mild hydronephrosis, ventriculoseptal defect	TOP (21)
3	18	47,XX,+18	SGA	Exomphalos, strawberry head	TOP (20)
4	18	47,XY,+18	SGA	Exomphalos, digital defects	TOP (19)
5	18	47,XY,+18	SGA	Exomphalos, digital defects, talipes, micrognathia, mild hydronephrosis	TOP (20)
6	20	46,XY,−14 +t(14q21q)	SGA	Nuchal oedema	TOP (22)
7	20	47,XX,+18	AGA	Diaphragmatic hernia, micrognathia, strawberry head, digital defects	TOP (22)
8	21	47,XY,+18	SGA	Diaphragmatic hernia, facial cleft	TOP (23)
9	21	47,XY,+18	SGA	"Absent stomach", digital defects, talipes	TOP (26)
10	21	47,XY,+18	SGA	Exomphalos, digital defects, ventriculoseptal defect, rocker-bottom feet	TOP (22)
11	22	47,XX,+18	SGA	Diaphragmatic hernia, facial cleft	TOP (22)
12	22	47,XX,+18	AGA	Digital defects, facial cleft, talipes	IUD (40)
13	23	47,XY,+18	AGA	Exomphalos, strawberry head, ventriculoseptal defect, digital defects	TOP (25)
14	24	46,XY,−14 +t(14q21q)	AGA	Ascites, skin oedema, mild hydronephrosis	TOP (25)
15	24	47,XY,+18	SGA	Diaphragmatic hernia, rocker-bottom feet	TOP (25)
16	24	47,XY,+18	SGA	Ventriculoseptal defect, talipes, strawberry head	TOP (25)
17	25	47,XX,+18	SGA	"Absent stomach", digital defects, strawberry head, micrognathia	TOP (26)
18	24	47,XY,+18	SGA	Strawberry head, micrognathia, digital defects	TOP (26)
19	27	69,XXX	SGA	Digital defects, microcephaly	TOP (27)
20	37	47,XY,+18	SGA	Posterior fossa cyst	NND
21	17	46,XY	AGA	Bilateral mild hydronephrosis	LB (41)
22	18	46,XY	AGA	Bilateral mild hydronephrosis	Continuing
23	18	46,XX	AGA	Exomphalos, kyphoscoliosis	TOP (22)
24	19	46,XY	AGA	Bilateral mild hydronephrosis	Continuing
25	19	46,XY	AGA	Bilateral severe hydronephrosis	TOP (22)
26	21	46,XY	AGA	Bilateral renal dysplasia, ascites	TOP (23)
27	21	46,XY	AGA	Ventriculoseptal defect, right multicystic renal dysplasia	LB (40)
28	21	46,XY	AGA	Bilateral mild hydronephrosis	LB (39)
29	21	46,XY	AGA	Bilateral mild hydronephrosis	LB (40)
30	21	46,XY	AGA	Bilateral severe hydronephrosis, kyphoscoliosis	TOP (23)
31	22	46,XX	AGA	Ventriculoseptal defect, bilateral mild hydronephrosis	LB (42)
32	24	46,XY	AGA	Bilateral severe hydronephrosis	TOP (27)
33	32	46,XX	AGA	Holoprosencephaly, facial cleft	NND
34	33	46,XY	SGA	Left moderate hydronephrosis, microcephaly	LB (39)

TOP: Termination of pregnancy.
IUD: Intrauterine death.
NND: Neonatal death.
SGA: Small for gestational age.
AGA: Appropriate for gestational age.
LB: Livebirth.

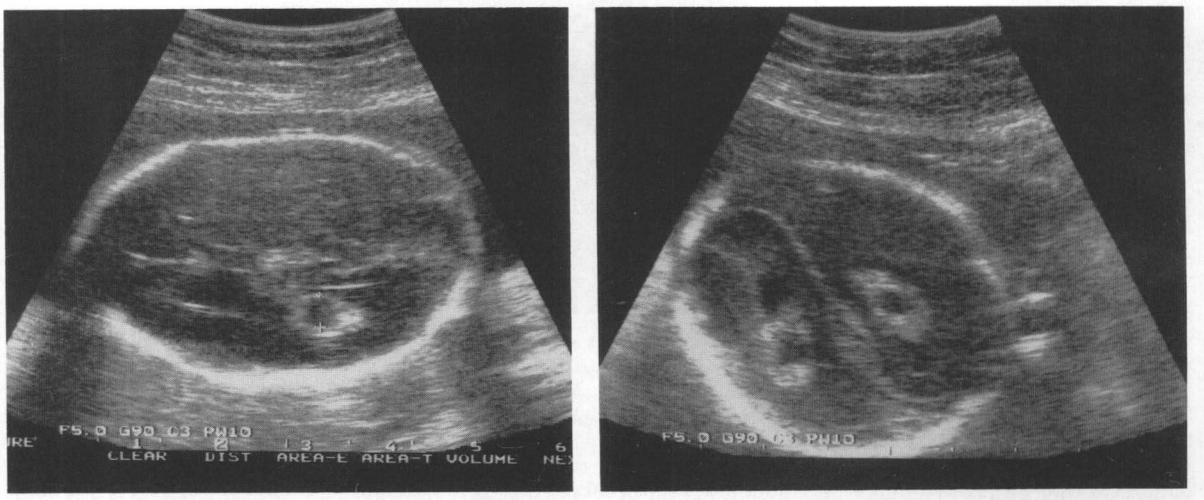

Figure 1. Coronal section demonstrating bilateral choroid plexus cysts.

these, one infant with Fallot's tetralogy underwent successful surgical repair and another with microcephaly, diagnosed in the post-natal period, died at 8 months of age. Five of the pregnancies were electively terminated because of the associated malformations. One infant with holoprosencephaly died in the neonatal period and two pregnancies are continuing.

In 49 of the 83 fetuses there were no additional malformations and in all but one case the cysts resolved by 28 weeks' gestation. In 12 pregnancies the mothers elected to have karyotyping performed and this was found to be normal. Forty-two pregnancies resulted in healthy normal livebirths, one pregnancy in an unexplained stillbirth at term with no detectable abnormality at post-mortem and one in an intrauterine death at 25 weeks, 9 weeks after a skin biopsy. Five pregnancies are continuing. In one case the cysts persisted throughout the antenatal period and were also present at the post-natal scan, but the infant, who is now 2 years old, has normal neurological development.

Discussion

The findings of this study confirm the association between choroid plexus cysts and chromosomal abnormalities. Although trisomy 18 is by far the commonest chromosomal defect, this is not exclusive as choroid plexus cysts were also present in one fetus with trisomy 13 and in two cases of translocation Downs' syndrome. All the chromosomally abnormal fetuses had additional malformations and in addition the majority of the fetuses were growth retarded. Therefore, the finding of choroid plexus cysts should prompt a diligent search for both major defects such as exomphalos and congenital diaphragmatic hernia but also for more subtle markers of trisomy 18 and 13 such as facial cleft, digital abnormalities, talipes, rocker-bottom feet and a strawberry shaped skull or prominent occiput. In the case of trisomy 21 the diagnosis may be suspected from a combination of features such as brachycephaly, relative shortening of the femur in relation to the biparietal diameter, nuchal skin oedema, atrio-ventricular septal defect, mild hydronephrosis and clinodactyly or hypoplasia of the midphalanx of the fifth finger.

In this series, chromosomal abnormalities were found in 59% of the fetuses noted to have choroid plexus cysts and additional malformations. These results are in agreement with the findings of Chitkara et al (1988) and Gabrielli et al (1989) who reported trisomy 18 in a total of five of seven cases of choroid plexus cysts in association with other structural anomalies seen at three referral centres. In these circumstances fetal karyotyping should be performed. Karyotyping is of value even in the third trimester of pregnancy, because knowledge that the fetus is chromosomally normal would allow the parents, obstetrician and paediatrician to discuss the appropriate mode, place and timing of delivery. Alternatively, if the fetus is chromosomally abnormal, the parents and attending obstetrician may decide that obstetric interventions, such as delivery by caesarean section, should be avoided. Fetal blood karyotyping can be achieved within 2–4 days, thereby alleviating parental anxiety associated with the 3–4 week delay in the UK if karyotyping from amniotic fluid. Karyotyping by placental biopsy using direct preparations of cytotrophoblastic cells can provide results in a few hours, but there is a significant risk of false positive results, especially for trisomy 18 and 13.

During the last 5 years in our centre, cordocentesis and fetal blood karyotyping was undertaken in 1265 cases. An abnormal karyotype was found in 204 cases. The most common were trisomy 18 ($n=56$), trisomy 13 ($n=19$), trisomy 21 ($n=36$) and triploidy ($n=30$). Choroid plexus cysts were present in 29%, 5%, 6% and 3% of the cases, respectively. Although the sensitivity is relatively low even for trisomy 18, it compares favourably with the sensitivity of screening for chromosomal

defects on the basis of maternal age alone, which is approximately 25%. Furthermore, choroid plexus cysts are useful markers because they are easily seen in the standard biparietal view which is obtained for all routine ultrasound scans. Alternative lesions detected by ultrasound screening that may potentially have much higher sensitivities for chromosomal abnormalities are presently not easy to detect at a routine examination. For example, congenital heart disease, such as ventricular septal defects, may be found in 90–99% of fetuses with trisomy 13 and 18 and in 50–80% of those with trisomy 21; however, these defects may be impossible to detect even in the second trimester by specialist echocardiographers (Allan et al, 1984: Copel et al, 1986).

Choroid plexuses are derived from neuroepithelial folds. The aetiology is poorly understood but has been thought to be a variant of normal development. However, in some fetuses, as in our case with microcephaly, choroid plexus cysts may be a manifestation of abnormal brain development. The choroid plexus is easily visualized from 9 weeks' gestation when it occupies almost the entire hemisphere. Thereafter, and until 24 weeks' gestation, there is a rapid decrease in both the size of the choroid plexus and of the lateral cerebral ventricle in relation to the hemisphere. Therefore, in normal fetuses cysts are most commonly seen during this phase of a relatively large choroid plexus, and the vast majority will resolve by 24 weeks. Although the natural history of the cysts in chromosomally abnormal fetuses is less well documented, because many of the pregnancies are electively terminated, it is possible that the high incidence of these cysts may be another manifestation of the delayed neurological development in such fetuses.

At present there is considerable controversy as to whether fetal karyotyping should be undertaken for choroid plexus cysts found in the absence of other malformations. There are three reported cases of trisomy 18 or 21 where choroid plexus cysts were the only antenatal finding, but a chromosomal anomaly was detected post-natally (Ricketts et al, 1987; Furness, 1987; Ostlere, 1989). Furthermore, the possibility of isolated choroid plexus cysts being the sole abnormality in fetuses with trisomy 18 is strongly suggested by the extremely worrying findings of a very careful pathological study by Fitzsimons et al (1989). Although 12 of 14 fetuses with trisomy 18 studied at post-mortem had other structural anomalies, bilateral choroid plexus cysts were the only abnormality in two of their fetuses. It was intimated that the risk of finding isolated choroid plexus cysts in a fetus with trisomy 18 was higher than the risk of a 35-year-old woman having a child with trisomy 21 and therefore karyotyping in these circumstances is justified. Although this is an attractive argument, the risk of fetal loss as a consequence of invasive techniques should not be underestimated, particularly as improving ultrasound technology and training will undoubtedly lead to increased detection of this condition. This is already well demonstrated in the study of Ostlere et al (1989) who reported a trebling in the incidence of choroid plexus cysts at 16–18 weeks' gestation with improving resolution of the ultrasound equipment used.

Fetal choroid plexus cysts are found in 0.18–2.3% of pregnancies (Clark et al, 1989; Gabrielli et al, 1989). Their detection should be an indication for detailed ultrasonography and the search for other markers of chromosomal defects. In the absence of additional malformations the parents should be made aware of the existing controversies concerning the association with chromosomal defects and allowed to have fetal karyotyping if they wish. Furthermore, serial scans should be undertaken to document resolution of the cysts and normal brain devlopment.

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