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Choroid plexus cysts and aneuploidy

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Abstract

The association of choroid plexus cysts with fetal aneuploidy, particularly trisomy 18, was first noted in 1986. Through the years there have been numerous reports on this subject, but no consensus has been reached with regard to chromosomal risk. In this review, we attempt to summarise published reports on second trimester choroid plexus cysts, with an emphasis on the strengths and weaknesses of each report. Based on these reports, additional malformations are a significant risk factor for aneuploidy and an indication for determination of fetal karyotype. The management of isolated choroid plexus cysts remains controversial.

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The choroid plexus develops in the lateral and fourth ventricles and is responsible for the formation of cerebrospinal fluid (CSF). The plexus is neuroepithelium covered villi which grow and become lobulated.[1] After 12 weeks, ultrasound easily shows these hyperechoic areas as the most prominent structure seen in the fetal brain. At 16 to 18 weeks' gestation the choroid plexus usually fills almost the entire lateral ventricles. Later, with involution and growth in the size of ventricles, the relative size of the choroid plexus diminishes.[1] Cysts may occur in the choroid plexus during the second trimester with maximal growth and entanglement of the villi, resulting in entrapment of CSF.

The first sonographic description of choroid plexus cysts (CPCs) is credited to Chudleigh *et al*[2] in 1984. They were considered benign and transitory until a possible association of these cysts with trisomy 18 was found.[3]

Trisomy 18 (Edwards syndrome) occurs in about 1:3000 to 1:5000 births.[4] Congenital heart disease in trisomy 18 is as high as 90%, most commonly VSD.[4] Growth restriction, craniofacial anomalies, and renal anomalies also occur frequently. The majority of fetuses with trisomy 18 will show either an anatomical or biometric anomaly on ultrasound. Two-thirds of those detected in the second trimester will spontaneously die in utero.[5] Of those live-born, 90-95% will succumb within the first year of life.[4]

The purpose of this review is to describe what is known about CPCs and their association with aneuploidy. By pooling world publications, we will attempt to determine the incidence of CPCs and their predictive value for aneuploidy. Finally, we will discuss what remains controversial and unclear and in need of further study.

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Methods

A Medline search of the English language publications from 1980 to 1997 was performed. All articles discussing the association of choroid plexus cysts and aneuploidy were evaluated. Case reports were excluded.

Articles fell into two general categories: (1) those discussing the incidence of choroid plexus cysts in the general population undergoing ultrasound examination with the resulting outcomes of these patients, and (2) those in which only patients with CPCs are discussed with the resulting outcomes.

Data were collected on the size, laterality, complexity, and disappearance of the CPC, as well as type of aneuploidy, other associated anomalies, and maternal age. Associated anomalies included only those detected prenatally and could either be anatomical (for example, clenched hand, heart defects) or biometric (for example, growth restriction or ventriculomegaly).

All 33 studies described women undergoing ultrasound evaluation between 14 and 24 weeks' gestation. Six of the 33 studies included women with gestational age greater than 27 weeks.[6–11]

Results and discussion

INCIDENCE OF CHOROID PLEXUS CYSTS

Those studies indicating the total number of scans performed and the number of those scans having a fetus with CPCs are shown in table 1. These data indicate that 1 in 122 (0.8%) fetuses scanned will have choroid plexus cysts (range 1 in 300 to 1 in 27.5).

PERCENTAGE OF FETUSES WITH TRISOMY 18 THAT HAVE CHOROID PLEXUS CYSTS

Those studies analysing a series of trisomy 18 fetuses and indicating the percentage with CPCs during the second trimester ultrasound examinations are shown in table 2. One in 1.8 (54.3%) fetuses with trisomy 18 will have a CPC.

ANEUPLOIDIES SEEN WITH CHOROID PLEXUS CYSTS

Each paper was reviewed for the various aneuploidies seen in association with CPCs. Of 203 reported abnormal karyotypes, there were 161 (79.3%) trisomy 18, 27 (13.3%) trisomy 21 including translocation Down syndrome, three (1.5%) trisomy 13, four (2.0%) triploidy, two (1.0%) 47,XXY, and six (3.0%) with unusual karyotypes each occurring only once.

Table 1 Incidence of choroid plexus cysts and aneuploidy in the presence of isolated CPCs and another anomaly

Ref	Author	Year	Incidence of CPCs: In population (No/total)	Incidence of CPCs: %	Incidence of aneuploidy with: Isolated CPC (No/total)	Incidence of aneuploidy with: Isolated CPC %	Incidence of aneuploidy with: CPC + other anomalies (No/total)	Incidence of aneuploidy with: CPC + other anomalies %
12	Achiron	1991	30/5400	0.6	1/29	3.5	1/1	100.0
13	Benacerraf	1989	—	—	0/38	0.0	—	—
14	Camurri	1989	10/3000	0.3	0/9	0.0	1/1	100.0
15	Chan	1989	13/513	2.5	0/13	0.0	—	—
16	Chinn	1991	38/1045	3.6	0/36	0.0	1/2	50.0
6	Chitkara	1988	41/6288	0.7	0/38	0.0	1/3	33.3
17	Chitty	1993	—	—	2/346	0.6	7/56	12.5
2	Chudleigh	1984	—	—	0/5	0.0	—	—
18	Clark	1988	5/2820	0.2	0/5	0.0	—	—
19	DeRoo	1988	17/2084	0.8	0/17	0.0	—	—
20	Gabrielli	1989	21/933	2.3	0/60	0.0	4/5	80.0
7	Gray	1996	208/18 861	1.1	0/192	0.0	7/26	26.9
8	Gross	1995	—	—	1/74	1.4	2/6	33.3
21	Gupta	1994	595/151 000	0.4	1/548	0.2	12/47	25.5
22	Hertzberg	1989	—	—	0/29	0.0	0/2	0.0
23	Howard	1992	51/4765	1.1	1/49	2.0	0/2	0.0
24	Kupferminc	1994	102/9100	1.1	4/98	4.1	3/4	75.0
9	Nadel	1992	—	—	0/220	0.0	12/14	85.7
3	Nicolaides	1986	—	—	0/1	0.0	3/4	75.0
10	Nicolaides	1992	—	—	1/49	2.0	33/72	45.8
25	Oettinger	1993	—	—	0/12	0.0	2/2	100.0
26	Ostlere	1990	100/11 700	0.9	0/91	0.0	3/9	33.3
27	Perpignano	1992	87/3764	2.3	5/86	5.8	1/1	100.0
28	Platt	1991	71/7350	1.0	0/67	0.0	4/4	100.0
29	Porto	1993	63/3247	1.9	2/59	3.4	4/4	100.0
30	Reinsch	1997	301/16 059	1.9	0/263	0.0	3/38	7.9
31	Rickets	1987	—	—	1/4	25.0	—	—
32	Shields	1996	—	—	7/274	2.6	9/11	81.8
33	Snijders	1994	387/17 583	2.2	2/277	0.7	43/110	39.1
11	Thorpe-Beeston	1990	—	—	0/49	0.0	20/34	58.8
34	Twining	1991	19/4541	0.4	0/16	0.0	2/3	66.7
35	Walkinshaw	1994	163/15 565	1.1	5/151	3.3	0/12	0.0
36	Zerres	1992	25/823	3.0	0/14	0.0	5/11	45.5
	Total		2347/286 441	0.8 1 in 122	33/3219	1.0 1 in 98	183/484	37.8 1 in 2.6

RISK OF ANEUPLOIDY WITH ISOLATED CHOROID PLEXUS CYSTS

Studies discussing the risk of aneuploidy in association with isolated CPCs are shown in table 1. One in 98 (1.0%) fetuses with an isolated CPC will have aneuploidy (range 0 to 1 in 4).

RISK OF ANEUPLOIDY WITH ADDITIONAL ANOMALIES

Studies listing the risk of aneuploidy in association with CPCs with at least one additional anomaly are shown in table 1. One in 2.6 (37.8%) fetuses with CPCs and an additional anomaly will have aneuploidy (range 0 to 1 in 1).

SIZE, LATERALITY, MULTIPLICITY, AND COMPLEXITY

Analysis of the data regarding size of CPCs is hampered by the different methods of reporting. For example, some papers listed a range size (minimum/maximum), some a mean and standard deviation, and some a minimum below which the cysts were not considered to be significant. Overall, the range of CPCs reported in euploid fetuses was 1 mm to 21 mm and 3 mm to 20 mm in aneuploid fetuses. A total of 725 (50.5%) of the reported cysts were unilateral and 710 (49.5%) were bilateral in the euploid fetuses, while in the aneuploid fetuses there were 30 (41.1%) unilateral and 43 (58.9%) bilateral cysts (p=0.147). Finally, there was no correlation between either multiplicity, multilocular, or complexity of the CPCs and aneuploidy.

Table 2 Incidence of CPCs seen by ultrasound evaluation in the 2nd trimester in fetuses with trisomy 18

Ref	Author	Journal	No of trisomy 18	No of CPC	%
12	Achiron	*Obstet Gynecol* 1991	5	5	100.0
13	Benaceraff	*Am J Obstet Gynecol* 1990	17	5	29.4
37	Bundy	*J Ultrasound Med* 1986	7	1	14.3
15	Chan	*Obstet Gynecol* 1989	0	2	0.00
16	Chinn	*J Ultrasound Med* 1991	0	2	0.00
6	Chitkara	*Obstet Gynecol* 1988	5	1	20.0
38	Fitzsimmons	*Obstet Gynecol* 1989	14	10	71.4
7	Gray	*Prenat Diagn* 1996	16	7	43.8
39	Nyberg	*J Ultrasound Med* 1993	29	11	37.9
33	Snijders	*Prenat Diagn* 1994	58	38	65.5
	Total		151	82	54.3 1 in 1.8

DISAPPEARANCE

Most CPCs disappear spontaneously during gestation, usually during the second trimester, as first described by Chudleigh *et al.*[2] This involution process appears to be part of the natural history of these cysts and has been described at the histological level.[1] However, ultrasound examination of the head of normal newborns has shown that up to 3% of normal neonates will have a small, unilateral CPC.[40] Disappearance of the cysts occurs both in euploid and aneuploid fetuses. There are a number of examples of CPCs in normal fetuses that persist until birth.[11 19] On the other hand, there are examples of cysts in aneuploid fetuses that disappear early.[26 27 41] There is no evidence that the time or lack of disappearance is related to the risk of aneuploidy.

MATERNAL AGE

Maternal age is related directly to the risk of aneuploidy. This is especially true for the trisomies and some sex chromosome aberrations.[42]

Table 3 Risk of trisomy 18 with relation to maternal age, CPCs, and additional anomalies

Maternal age (y)	*Isolated CPCs*	*CPC + additional anomaly*
20–24	1 in 2950	1 in 225
25–29	1 in 2300	1 in 175
30–34	1 in 1300	1 in 100
35–39	1 in 470	1 in 35
40–44	1 in 100	1 in 10

Adapted from ref 33 with permission.

Age specific rates are available. The risk of trisomy 21 and trisomy 18 increases with maternal age with the former being five to seven times more prevalent. For example, at second trimester amniocentesis, a woman aged 35 has a 1 in 263 risk for trisomy 21 and a 1 in 2000 risk for trisomy 18.[42] If one assumes that CPCs occur in fetuses with trisomy 18 at the same frequency regardless of maternal age, then the incidence of CPCs should increase as maternal age increases.

Unfortunately, maternal age was not consistently reported. Several reports have shown that CPCs in an otherwise normal fetus occur in women of all maternal ages.[2 19 24 29 33] One group reporting on 16 women with CPCs and aneuploidy found no difference between their maternal age (mean 29.8 years, SD 8.1) and those with CPCs and normal karyotype (30.6 years, SD 6.2).[32] In the same report the mean maternal age of the seven women with isolated CPCs and aneuploidy was 18.9 years (SD 2.3), while for the nine fetuses with CPCs and another anomaly, it was 20.4 years (SD 3.7). In another report[7] there was no difference in mean maternal age between those mothers with fetuses with CPCs and normal karyotype (31 years), CPCs with normal karyotype but with other anomalies (31 years), and those with CPCs and trisomy 18 (31 years). However, given the diversity of the reports, it is not possible to do statistical comparisons.

One study was able to show that in those fetuses with CPCs (n=387), the incidence of trisomy 18 was significantly associated with maternal age.[33] Risk estimates for trisomy 18 were constructed based on the assumptions that (1) the risk of trisomy 18 increases with maternal age; (2) the incidence of CPCs is 1%; (3) 50% of fetuses with trisomy 18 will have CPCs at mid gestation; and (4) the risk of trisomy 18 increases when additional fetal anomalies are found (table 3).

Table 4 Age specific risks of trisomy 18 with isolated CPC and normal maternal triple screen

Maternal age	*Isolated CPC*	*Isolated CPC + normal maternal triple screen*
30	1 in 432	1 in 1574
31	1 in 378	1 in 940
32	1 in 324	1 in 806
33	1 in 273	1 in 679
34	1 in 225	1 in 560
35	1 in 183	1 in 454
36	1 in 146	1 in 363
37	1 in 115	1 in 287
38	1 in 92	1 in 223
39	1 in 70	1 in 173
40	1 in 54	1 in 133
41	1 in 42	1 in 102
42	1 in 32	1 in 78

Adapted from ref 43 with permission.

Addressing the question similarly, Gratton *et al*[43] calculated age specific risks using the assumptions that (1) 30% of fetuses with trisomy 18 will have CPCs, (2) 80% of fetuses with trisomy 18 will have additional ultrasonographic anomalies, and (3) maternal triple screen detects 60% of fetuses with trisomy 18 independent of CPC status. Their opinion was that it is unlikely that ultrasonographic detection of CPCs and maternal serum triple screen identify the same fetuses with trisomy 18, an assumption unsupported as yet by data. Their results are shown in table 4. Using their calculations, amniocentesis would be recommended to women aged 33 and above for those with isolated CPCs, and aged 37 and above if the maternal serum triple screen were also normal.

Recommendations

Twenty-three reports gave recommendations. All regarded CPCs as an indication for a detailed anomaly scan. In the face of CPCs and another anomaly, all suggested fetal karyotyping. When the CPC was isolated, 11 authors said they would not recommend invasive testing,[2 7 9 11 16 17 21 23 25 30 33] four said they would not unless the cysts appeared unusual (large, bilateral, complex, or persistent),[6 22 26 34] and nine said they would in all cases.[3 12 24 27 29 32 35 36]

Other parameters

There are other parameters that probably affect the detection of CPCs and the calculated risk of aneuploidy. For example, ultrasonography has become more refined, with better machines and more experienced operators. These two factors probably would increase detection of both CPCs and additional anomalies. On the other hand, not all sonographers search for the same group of anomalies (for example, clenched hands).

The statistical analysis performed in table 1 is based on the assumption that the various reports mentioned are comparable. The differences in population, machines, and sonographers is certainly confounding. However, although the articles discussing the incidence of CPC detection were published between 1988 and 1997 (table 1), an increase in trend cannot be found.

Finally, maternal serum triple screen can reportedly detect up to 60% of trisomy 18 in the absence of an open defect.[44] There have not been any studies exploring the combination of CPCs on ultrasound and a positive maternal serum triple screen for detection of aneuploidy.

Summary

CPCs should be considered an indication to search for other anomalies. Although the incidence is 1 in 122 pregnancies, fetuses with trisomy 18 display CPCs at least 50% of the time. The presence of associated sonographic anomalies, whether biometric or anatomical, increases the risk of aneuploidy by over 35 times. Maternal age also correlates with aneuploidy. Trisomy 18 and trisomy 21 are similar in that by limiting invasive testing to

above a certain maternal age (for example, 35 years), many cases with chromosomal abnormalities will be missed.

Isolated CPCs have an overall detection rate for aneuploidy of 1 in 98, meaning a false positive rate of about 99%. Controversy remains whether an isolated CPC is an indication for invasive testing. We suggest that in the presence of another risk factor, whether it be an abnormal maternal serum triple screen, a previous child with aneuploidy, advanced maternal age, or additional detected anomaly, the patient should be made aware of the higher risk of aneuploidy and the benefit of prenatal testing. At present, with an isolated CPC, we attempt to counsel the patient in a non-directive fashion similar to those with a trisomy 18 pattern on maternal serum screening.[45] The mother is told that studies indicate that the risk of aneuploidy is about 1 in 100, although her age influences this rate. All patients are offered amniocentesis for definitive diagnosis. Serum triple screen should be obtained if not available and the mother is less than 20 weeks' gestation. For those electing to continue the pregnancy without invasive testing, we do suggest serial fundal height examinations and a repeat ultrasound for growth and anomalies before 24 weeks to allow the patient to reconsider amniocentesis.

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