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Risk of Chromosome Abnormalities in the Presence of Bilateral or Unilateral Choroid Plexus Cysts

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Key Words
Choroid plexus cyst · Chromosome abnormality · Ultrasound · Genetic amniocentesis · Karyotyping · Chorionic villus sampling

Abstract
Objectives: To evaluate the rate of chromosome abnormalities in cases of uni- and bilateral choroid plexus cysts (CPCs). ***Methods:*** A total of 10,875 ultrasound (US) examinations were performed in the second trimester, and 435 cases with CPC (4%) were found. After genetic counseling, 45 patients decided not to undergo karyotyping. The authors performed a chromosome analysis in 390 cases of CPCs. ***Results:*** The total risk of chromosome abnormalities was 3.59% (n = 14) and risk of trisomies was 2.05% (n = 8). Trisomy 18 was found in 6 cases (1.54%), trisomy 21 in 1 case (0.26%), and trisomy 9 in 1 case (0.26%). The risk of 45,X karyotype was 0.77% (n = 3). One case of 47,XXY karyotype and 2 cases with other chromosome abnormalities were found. In 212 unilateral cases there were 7 with chromosome abnormalities (3.3%). In 178 bilateral cases there were 7 with abnormal karyotypes (3.93%). The CPC was associated with additional fetal US anomalies (with or without polyhydramnios/oligohydramnios) in 112 cases; chromosome abnormalities were detected in 4 cases (3.57%). 66 cases were associated with polyhydramnios/oligohydramnios but not with other fetal US anomalies; 3 cases of abnormal karyotypes were found (4.55%). The CPC was isolated in 212 cases and 7 cases were associated with chromosome disorders (3.3%). ***Conclusions:*** US plays an important role in prenatal diagnostics. Further genetic counseling is recommended in cases with CPCs.

Introduction

The minor anomalies found during prenatal ultrasound (US) are very important in the screening of chromosome abnormalities. The question is raised whether minor anomalies justify intrauterine karyotyping. Prenatal diagnostic invasive methods include genetic amniocentesis and chorionic villus sampling. In our study we have examined the role of choroid plexus cyst (CPC) from cranial and cerebral US anomalies.

In cases of CPCs, mainly in isolated cases, the data in the literature are controversial, and there are different opinions about the isolated presence of CPCs and about whether it justifies in itself the invasive diagnostic procedures (table 1). According to the data of other authors [1, 2], CPCs mainly increase the risk for trisomy 18. According to certain studies the risk level does not depend on whether the anomaly is uni- or bilateral, but other studies show that the larger the anomaly (>10 mm) the higher the

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Table 1. Choroid plexus cysts

Group (first author)	Year	Cases	Chromosome abnormalities	
			n	%
Nicolaides	1986	4	3	75.00
Achiron	1991	30	2	6.67
Chinn	1991	38	1	2.63
Platt	1992	62	4	6.45
Nadel	1992	234	12	5.13
isolated		220	0	0.00
with other abnormalities		14	12	85.71
Walkinshaw	1994			
isolated		152	4	2.63
Nava	1994	176	8	4.55
Gonen	1995	108	0	0.00
Gray	1996	208	7	3.37
Geary	1997	84	3	3.57
isolated		78	0	0.00
with other abnormalities		6	3	50.00
Bakos	1998	108	3	2.78
Chitty	1998	658	14	2.13
isolated		603	3	0.50
with other abnormalities		55	11	20.00
Ghidini	2000			
isolated		765	13	1.70
Coco	2004	366	2	0.55
isolated		311	0	0.00
with other abnormalities		55	2	3.64
Sahinoglu	2004	109	4	3.67
isolated		102	3	2.94
with other abnormalities		7	1	14.29

risk [3, 4]. Certain authors suggest the 2- to 2.5-mm cut-off value [5], while others determined the 5-mm limiting value [3]. The cysts resolve practically every time, so the absence of the anomaly on a repeated US examination does not indicate a decrease in the risk [6].

Chudleigh et al. [7] were the first to describe cysts in the fetal choroid plexus. In a study including a small number of cases, Nicolaides et al. [8] were the first to draw attention to the connection between the positive US finding of CPCs and chromosome abnormalities. Thereafter, more authors demonstrated that fetal CPCs mainly increase the risk of trisomy 18, and to a lesser degree the risk of trisomy 21.

Achiron et al. [9] demonstrated two trisomy 18 cases by chromosome analysis of 30 CPC cases (6.67%); in 1 case the CPC was associated with other US anomalies. Chinn et al. [10] found 1 case of triploidy from 38 cases. Platt et al. [11] found 4 cases of chromosome abnormalities from 62 cases (6.45%); in 3 cases it was trisomy 18 and in 1 case trisomy 21. Nadel et al. [12] demonstrated 12 cases of abnormal chromosomes from a larger number of cases (n = 234), 11 of which were trisomy 18 (4.7%) and 1 case of triploidy, but of the 234 cases there were 220 of isolated CPC, and in these cases the authors did not detect any chromosome abnormalities.

Walkinshaw et al. [3] demonstrated 4 cases (2.63%) of chromosome anomalies out of 152 isolated CPC cases; in 3 cases of trisomy 18 (1.97%) and 1 case of trisomy 21. Nava et al. [13] found 8 chromosome abnormalities in 176 cases (4.55%). Four cases of trisomy 18 (2.27%), 2 cases of trisomy 21 (1.14%), 1 case of 47,XXY karyotype, and 1 case of another chromosome anomaly. Of the trisomy 18 cases there was 1 case of isolated CPC, while in 3 cases the abnormality was associated with other US findings. Gonen et al. [14] demonstrated no abnormalities in the course of intrauterine karyotyping among 108 CPC cases.

Gray et al. [4] performed karyotyping in 208 cases and detected abnormal karyotypes in 7 cases, each case was trisomy 18 (3.37%). Geary et al. [15] examined 84 cases of

CPC, 78 were isolated and they found no chromosomal aberration; in 6 cases with other US anomalies they found 3 cases (50.00%) of trisomy 18. Bakos et al. [16] found 3 abnormal karyotypes out of 108 examined cases (2.78), 1 case was trisomy 18, 1 was trisomy 13, and 1 inversion of the chromosome 9.

With a larger number of cases, Chitty et al. [17] examined separately the isolated cases and the cases associated with other US anomalies. In 603 the CPC was not associated with other US abnormalities, and in 3 cases (0.5%) they found abnormal karyotypes (each was trisomy 18); in 55 cases the abnormality was associated with other US findings, and in 11 cases (20%) they detected abnormal karyotypes (in 9 cases trisomy 18, in 1 case trisomy 21 and in 1 case 47,XXX karyotype). With a similarly large number of cases, Ghidini et al. [18] examined the incidence of chromosome abnormalities in cases of CPCs; they only examined the isolated cases (n = 765) and found abnormal karyotypes (trisomy 18) in 13 cases (1.7%).

Coco and Jeanty [19] in 2004 examined separately the isolated cases and those associated with other abnormalities, the cases associated with minor and major US anomalies. In isolated cases (n = 311) and in associated cases with minor anomalies (n = 43) they did not find abnormal karyotypes. In the 2 detected cases of trisomy 18, the CPC was associated with major anomalies (16.67% from 12 cases). Sahinoglu et al. [20] performed karyotyping in 109 cases due to CPC; in 102 cases it was an isolated anomaly and in 3 cases they found chromosome abnormalities (2.94%). In 7 cases CPCs were associated with other US anomalies, and they found chromosome abnormality in 1 case (14.29%); in 4 cases the abnormal karyotype was trisomy 18.

Methods

In a retrospective study during a 10-year period, 10,875 US examinations were performed in an unselected population in the second trimester at genetic counseling of the First Department of Obstetrics and Gynecology Semmelweis University. During this period we found 435 cases with CPC. In this study we investigate the chromosome abnormalities detected in cases with prior CPCs.

The US examinations were performed using ATL Ultramark 4 and Ultramark 9 (3.5-MHz curvilinear transducer; Advanced Laboratory Technology, Bothwell, Wash., USA). The examinations were carried out on the basis of the professional protocols of the Hungarian Society of Ultrasound in Obstetrics and Gynaecology.

In cases with positive US findings the couples were fully informed about the risk of chromosome abnormalities. Following counseling, with full knowledge about the risk of the invasive intervention, the couples decided whether or not they wanted to undergo the examination. After detailed counseling, 45 patients declined karyotyping. We therefore performed a chromosome analysis in 390 cases of CPCs. The majority of the invasive interventions carried out for chromosome analysis were US-guided transabdominal genetic amniocentesis, which were performed between 15 and 21 weeks of pregnancy. The minority of the chromosome analyses was chorionic villus sampling.

The samples from the amniotic fluid and chorion villi were cytogenetically processed. We examined the amniotic fluid samples after cell culturing and the chorionic villus samples without culturing (utilizing the direct mitotic activity) or after culturing. By arresting the mitotic cell division in the metaphases, microscopic examination and karyotyping of the chromosomes is made possible. In some cases the demonstration of numerical chromosome abnormalities was confirmed by molecular genetic examination by quantitative fluorescent PCR (QF-PCR) technique.

Table 2. Choroid plexus cysts

	Unilateral	Bilateral	Total
Cases	212	178	390
Mean	5.8189	7.3006	6.4951
Median	5	7	6
SD	2.5425	3.4000	3.0517

Results

During a 10-year period, 10,875 US examinations were performed in the second trimester, and we found 435 cases with CPC (4%); 45 patients decided not to undergo karyotyping. According to the information we had about the pregnancy in 20 cases, none had chromosome abnormalities. We performed a chromosome analysis in 390 cases of CPCs; in 212 the abnormality was unilateral and in 178 it was bilateral. The average diameter of the plexus cysts was 5.8 $\pm$ 2.5 mm in the unilateral cases, and in cases of bilateral cysts we calculated the size of the larger cyst where the average value was 7.3 $\pm$ 3.4 mm ($p < 0.001$) (table 2).

We examined the incidence rate of the bilateral CPCs and the correlation with the size of the cysts. As the size of the cyst increased, the incidence rate of the bilateral cases also increased. The size of the plexus cyst and the incidence rate of the bilateral abnormalities are demonstrated in figure 1. Examining the distribution of the different sizes of cysts, we found a near normal distribution (fig. 2). The mean value of the normal distribution was 6 mm. When we examined the distribution of the uni-

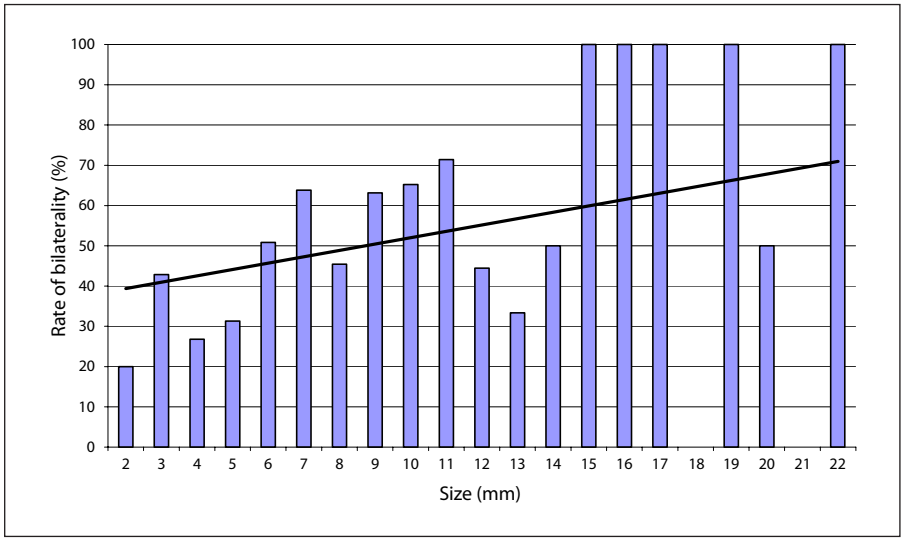

Fig. 1. Rate of bilaterality and size of CPCs.

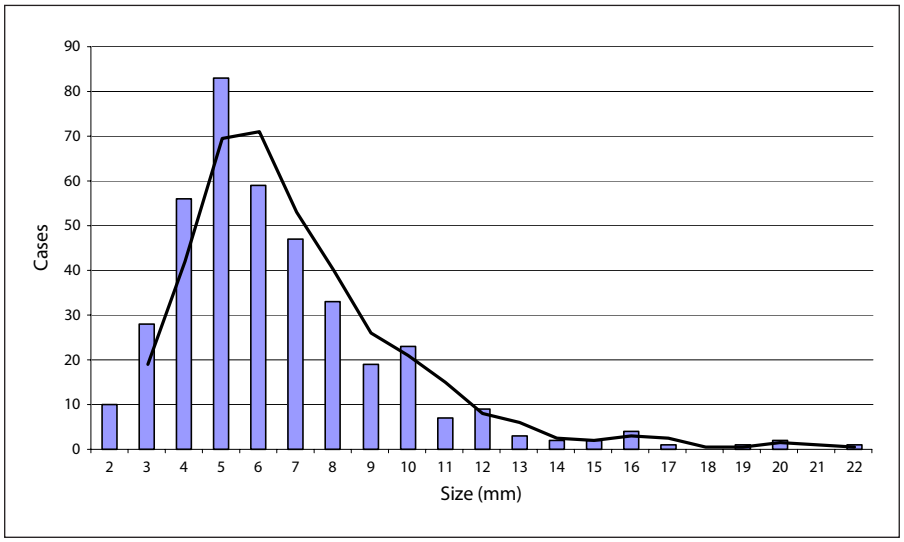

Fig. 2. Size distribution of CPCs.

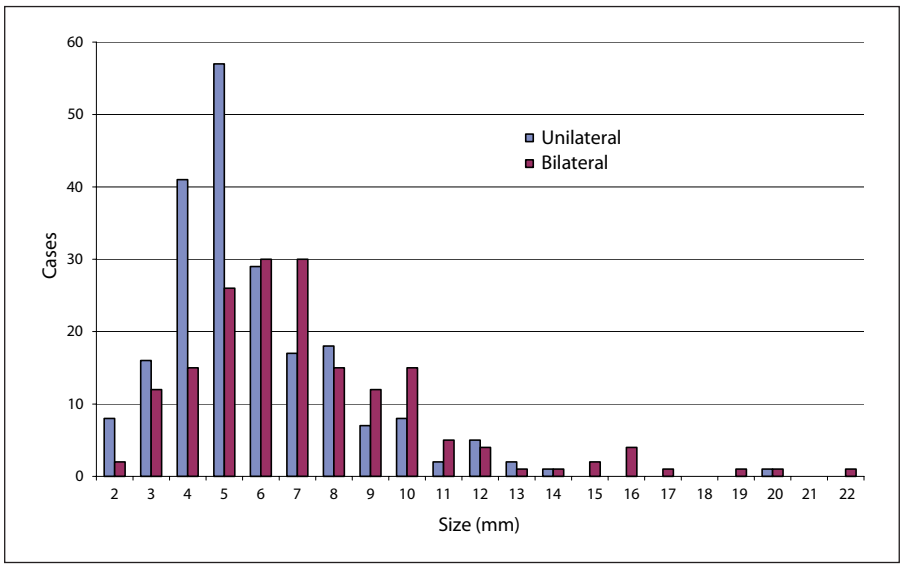

Fig. 3. Size distribution of uni- and bilateral CPCs.

Table 3. Choroid plexus cysts and chromosome abnormalities

	Cases	Chromosome abnormalities	
		n	%
Unilateral	212	7	3.30
Bilateral	178	7	3.93
Total	390	14	3.59

Table 4. Type of chromosome abnormalities

	Unilateral	Bilateral	Total
Trisomy 18	1	5	6
Trisomy 21	1	0	1
Other trisomy	0	1[a]	1
45,X	3	0	3
47,XXY	1	0	1
Other	1[b]	1[c]	2

[a] Trisomy 9; [b] 46,XX/46,XY; [c] 46,XY/47,XXY/47, XYY.

Table 5. Size of choroid plexus cysts and type of chromosome abnormalities

Size mm	Unilateral	Bilateral
2		
3		
4	trisomy 21	
5	47XXY 45,X	
6	45,X	trisomy 9
7	trisomy 18	46XY/47XXY/ 47XYY
8	46XX/46XY 45,X	
9		
10		trisomy 18
11		
12		trisomy 18 2 ×
13		
14		
15		
16		
17		
18		
19		trisomy 18
20		
21		
22		trisomy 18

and bilateral plexus cysts separately, the mean value (median) of the normal distribution of the unilateral cysts was 5 mm, while in the case of bilateral cysts it was 7 mm (fig. 3).

In the case of CPC we detected abnormal karyotypes in 3.59% (table 3). In unilateral cases the rate of the abnormal karyotypes was 3.3%, in bilateral cases this rate was 3.93%. We also examined the types of chromosome abnormalities. The detected abnormal karyotypes are demonstrated in table 4. Altogether, we found abnormal karyotypes in 3.59% (n = 14), the risk of trisomies was 2.05% (n = 8). We found trisomy 18 in 6 cases (1.54%), trisomy 21 in 1 case (0.26%), and trisomy 9 in 1 case (0.26%). The risk of 45,X karyotype was 0.77% (n = 3). We found 1 case of 47,XXY karyotype (0.26%) and 2 cases (0.51%) of other chromosome abnormalities (46,XX/46,XY mosaicism, 46,XY/47,XXY/47,XYY mosaicism).

In cases with CPCs, 42.86% of the chromosome abnormalities were trisomy 18, while 21.43% of cases were monosomy X. Examining the various karyotypes, we found that the chromosome abnormalities occurred in different rates in the uni- and bilateral cases, and the incidence rate was different in cases of the various sized plexus cysts. The incidence of chromosome abnormalities is demonstrated in table 5 in uni- and bilateral cases, as a function of the plexus cyst size. Each trisomy 18 occurred in cases of CPC over the mean value ≥7 mm. 83.33% of the trisomies 18 (5/6 cases) were detected in cases of cyst size ≥10 mm, and in these the plexus cyst was bilateral. On the other hand, when associated with monosomy X, the CPC was always unilateral and the size was <10 mm. With the exception of the trisomy 18, all of the chromosome abnormalities occurred in cases of plexus cysts <10 mm.

The incidence rate of the chromosome abnormalities in correlation with the maternal age is demonstrated in table 6. Each chromosome abnormality was detected under the age of 35 years, therefore not in the age groups bearing a high age-related risk.

We examined the CPC cases when associated with other US findings and also isolated cases (table 7). In 112 cases the CPC was associated with other fetal US findings (with or without polyhydramnios/oligohydramnios), and in 4 cases we detected abnormal karyotypes (3.57%): in 3 cases trisomy 18, and in 1 case monosomy

Table 6. Chromosome abnormalities in different maternal ages

Age	Unilateral	Bilateral
16		
17		
18		
19	46XX/46XY	trisomy 9
20	47,XXY	trisomy 18
21		
22		
23		
24	trisomy 18	
25		
26		46XY/47XXY/ 47XYY
27	45,X	
28	45,X	
29	trisomy 21	trisomy 18
30	45,X	trisomy 18
31		
32		trisomy 18
33		trisomy 18
34		
35		
36		
37		
38		

X. The associated fetal anomaly, with other abnormalities, was ventriculomegaly in 58 and pyelectasia in 31 cases, and in 19 cases subcutaneous edema was detected (hydrops in 1, nuchal edema in 18). In 66 cases poly- or oligohydramnios was associated with the CPC without other fetal US anomalies, and in 3 cases we detected abnormal karyotypes (4.55%), trisomy 18 in 2 cases and monosomy X in 1 case. The CPC was isolated in 212 cases, that is it was not associated with other fetal US findings and/or poly/oligohydramnios, and in 7 cases we found chromosome abnormalities (3.3%), 1 case of trisomy 18, trisomy 21, trisomy 9 and monosomy X and 47,XXY karyotype.

Discussion

In the course of prenatal diagnostics it is common opinion that performing an invasive intervention is justified if the risk of the chromosome abnormality is higher than the risk of abortion caused by the invasive intervention. In our department, the risk of fetal loss 4 weeks after the procedure is 0.5% in cases of genetic amniocentesis, and 1.7% in cases of transabdominal chorion biopsy. These rates are lower than the 1 and 2–2.5% risks quoted in the literature. In the course of chromosome analyses in cases of CPC we found abnormal karyotypes in 3.59%. We examined the uni- and bilateral cases as well as the isolated and associated cases.

Table 7. Isolated cases and cases with other anomalies

	Cases	Chromosome abnormalities	
		n	%
With other fetal anomalies	80	3	3.75
With other fetal anomalies + poly/oligohydramnios	32	1	3.13
Poly/oligohydramnios	66	3	4.55
Isolated	212	7	3.30
Total	390	14	3.59

In cases of CPC, mainly in isolated anomalies, the data in the literature are conflicting whether the presence of the CPC in itself justifies the invasive procedure [3, 17–20]. According to the literature, the CPC is an anomaly which increases the incidence rate of trisomy 18, and to a lesser extent the occurrence of trisomy 21 [3, 9, 11, 13]. In our study, corresponding with data in the literature, we found abnormal karyotypes in 3.59% and detected a higher rate of trisomy 18 (6 cases, 1.54%). We detected X-monosomy in 3 cases (0.77%), trisomy 21 in 1 case (0.26%), and 47,XXY karyotype also in 1 case (0.26%).

Performing 390 chromosome analyses of CPC cases, in 112 cases the CPC was associated with other fetal US anomalies, in 66 cases only poly- or oligohydramnios was associated with the plexus cyst, in 212 cases there were no other positive US findings. In our study there was no significant difference either in the cases associated with other positive US findings or in the non-associated cases. In cases of uni- and bilateral malformations there was no significant difference (3.3 and 3.93%). According to the results, the uni- and bilateral malformations as well as the isolated cases also warrant chromosome analysis.

At the genetic counseling it is very important to give appropriate information to the couple and to emphasize the fact that CPC also occurs in normal pregnancies, and if no abnormal karyotype is detected, the anomaly in itself does not give cause for anxiety.

Conclusions

According to our examinations we could establish that in cases of CPC further counseling is recommended, and if the couple decides to undergo the chromosome examination, karyotyping is recommended. We demonstrated abnormal karyotypes in 3.59%.

In cases of certain bilateral anatomical features the risk of the chromosome abnormalities is different in uni- and bilateral anomalies. According to our examinations, karyotyping is justified both in uni- and bilateral abnormalities; we detected abnormal karyotypes in 3.3% of unilateral cases and in 3.93% of bilateral cases. The difference was not significant, and on the basis of our results we established that in cases of uni- and bilateral CPCs a chromosome analysis is recommended.

In some cases of certain US findings, the opinions formed after genetic counseling are determined by the fact whether the US finding is isolated or associated with other findings. We could establish that a chromosome analysis is recommended both in isolated and associated cases of CPC. By examining the distribution of the trisomies and other chromosome abnormalities, we established that in cases of CPC, mainly the risk of trisomy 18 and monosomy X is increased, but we also found trisomy 21 and 47,XXY karyotype.

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