Congenital Subependymal Pseudocysts: Own Data and Meta-Analysis of the Literature*

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Abstract

Background: Congenital subependymal pseudocysts are incidental findings that are found in 0.5–5.2% of neonates during postmortem examination or head ultrasonography. In our institution we detected 10 neonates with CSEPC.

Objective: To investigate associated etiological factors, morphologic characteristics and outcome of CSEPC.

Methods: We performed a meta-analysis of the literature on CSEPC (1967–98), including our 10 cases.

Results: A total of 256 cases of CSEPC were analyzed. Ultrasound diagnosed 77.6% of CSEPC; 48.8% were bilateral and 53.4% were located in the caudothalamic groove or head of caudate nucleus. Altogether, 93.5% resolved during 1–12 months of ultrasonographic follow-up. Compared to the general neonatal population, the following features were more prevalent in the CSEPC population: prematurity, maternal vaginal bleeding, preeclamptic toxemia, intrauterine growth restriction, asphyxia, fetal cytomegalovirus and rubella infections, congenital malformations, chromosomal aberrations, infant mortality, and neurodevelopmental handicap. The risk for neurodevelopmental handicap was significantly higher when CSEPC were associated with fetal infections, IUGR, malformations and chromosomal aberrations, or persistence of CSEPC during follow-up. CSEPC infants without any of these four conditions had a low risk for neurodevelopmental handicap.

Conclusions: CSEPC are morphologic features of various underlying conditions encountered in the fetus. Association of CSEPC with IUGR, fetal infections, malformations and chromosomal aberrations or persistence of CSEPC indicates a higher risk for future neurodevelopmental handicaps, probably because of the deleterious effects on the fetal brain that are inherent in these conditions. A favorable outcome is expected in the absence of these risk factors.

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The survival rates of high risk neonates have significantly increased during the last two decades. The use of head ultrasonographic examination has become routine in neonates. Congenital subependymal pseudocyst is an uncommon finding that is diagnosed by ultrasound of the neonatal brain. Prior to 1980, CSEPC were incidentally detected during postmortem examination of neonates [1–6]. Since 1980, the growing use of head ultrasonography in sick neonates has led to increased detection of CSEPC [7–23]. This resulted in mounting interest regarding the etiology and prognosis of this finding. In four large prospective studies, CSEPC was sonographically diagnosed in 0.5–5% of healthy term neonates [10,22], in 5.23% of sick premature infants [9], and in 4.1% of all admissions to the neonatal intensive care unit [16].

It should be emphasized that CSEPC are congenital and could be diagnosed immediately after birth using head ultrasonography. Acquired cysts due to hemorrhage or infarctions that occur after birth are beyond the scope of this study. CSEPC are classified as pseudocysts because they lack the ependymal cell lining or any specific limiting membrane found in true cysts. CSEPC probably result from an intrauterine injury to the vulnerable germinal matrix in the periventricular subependymal area, mostly due to vascular events such as hemorrhage or infarction or due to congenital infection, mainly cytomegalovirus [1–5]. During fetal life, the subependymal germinal matrix zone is relatively large; it becomes smaller at 32–34 weeks of gestation, and any injury to this region in early gestation might subsequently result in a pseudocyst [4].

Histopathological examination of CSEPC reveals the following features: immature and undifferentiated lining cells, buds of immature cells protruding into the lumen, cavities bounded by thick glial meshwork, subependymal fine trabeculae, destruction of cells, non-homogenous matrix, macrophages, and iron staining representing an old hemorrhage in some cases [4]. Macroscopically, CSEPC are seen as isolated large cavities that are limited by pseudo-capsules, or as bilateral symmetrical cavities or irregular thin trabeculated honeycomb-like cavities [4].

Sonographically, CSEPC could be unilateral or bilateral, single or multiple. Although CSEPC might be located through-

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CSEPC = congenital subependymal pseudocysts

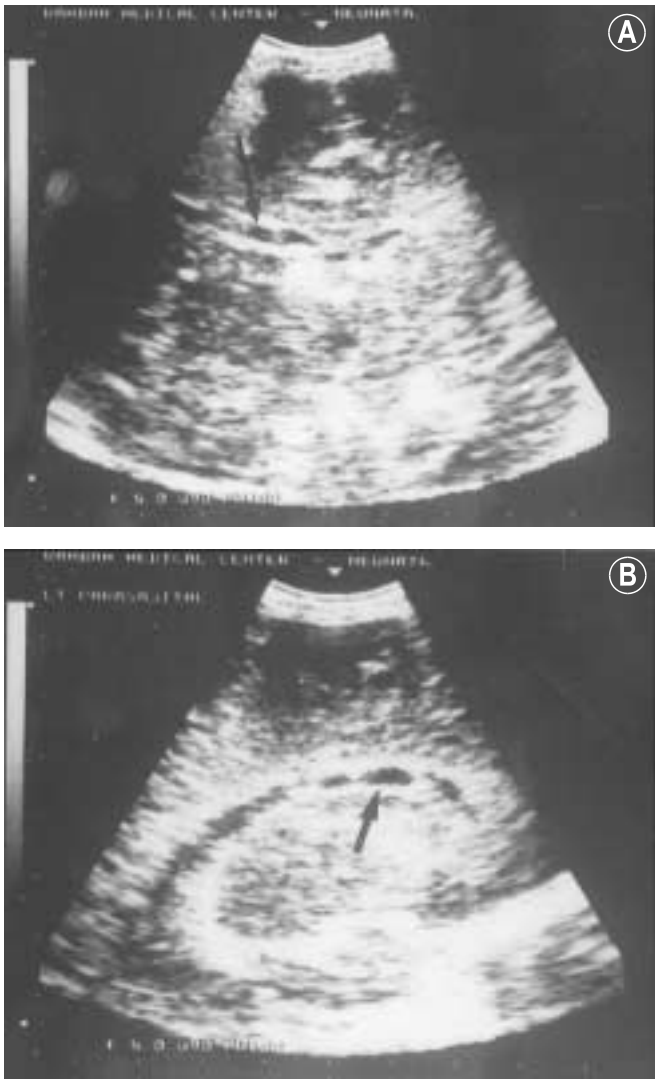

Figure 1. Ultrasound scan of brain at 12 hours of age. **[A]** coronal section showing a subependymal pseudocyst located anterolateral to the frontal horn of the lateral ventricle (arrow); **[B]** the same finding in a parasaggital section (arrow).

out the periventricular area, they are usually seen in the caudothalamic groove or adjacent to the head of caudate nucleus [Figure 1]. Since CSEPC develop within the germinal matrix, and given that this matrix gradually resolves during fetal life, we speculate that the location of CSEPC might indicate the timing of injury, i.e., the further from the caudothalamic groove the earlier the injury occurred in fetal life.

Among sick neonates admitted to our neonatal intensive care unit in 1990–97, we found 10 neonates with CSEPC as demonstrated by head ultrasound. Published reports of CSEPC include rather small series of patients, and each alone is insufficient as a source of information regarding the etiology, associated perinatal factors, morphologic characteristics and outcome of CSEPC. In order to obtain a more comprehensive picture of this condition, we performed a meta-analysis of reports of CSEPC in the literature.

Methods

Our data

During an 18 month period (1996–97), we prospectively performed head ultrasonographic examinations during the first 36 hours of life on all 340 sick neonates admitted to our NICU using a 5-MHz transducer (Model SSD-620, ALOKA Co., Japan). CSEPC were detected in eight neonates (2.3%), a rate that conforms with that of Yamashita et al. [16], in all NICU admissions. Two additional CSEPC cases were found by a retrospective review of the charts of all admissions to the NICU during 1990–96. CSEPC detection rates in the two periods differed because in the years 1990–96 head ultrasound was performed only for sick neonates with suspected neurological abnormalities, while during 1996–97 routine bedside ultrasound was feasible in the NICU and all admitted neonates were screened ultrasonographically for brain abnormalities.

We collected relevant data on our 10 neonates with regard to their perinatal course, possible fetal infection and abnormal findings on physical examination. All 10 infants underwent neurodevelopmental assessment at 2–18 months of age.

Meta-analysis of literature on CSEPC

We conducted a thorough review of the literature on CSEPC in terms of the reported neonatal, radiological and neurological characteristics of this lesion (Medline search, EBSCO Publishing, National Library of Medicine, 1966–99). We found 23 reports consisting of limited series of CSEPC and describing a total of 246 CSEPC cases [1–23]. These reports were either prospective or retrospective and included different sub-populations. In the prospective studies all admitted neonates were sonographically screened for brain abnormalities, including CSEPC. Some of these studies were carried out in the normal nursery, but the majority was performed in the NICU. In the retrospective studies, cranial ultrasound had been performed only for very sick neonates and their records were reviewed for brain sonographic abnormalities.

We performed a *comprehensive* summary that included all the cases described in all the reports, to which we added our 10 CSEPC infants; this totaled 256 CSEPC cases in 24 reports. We summarized the data on diverse variables that might be associated with CSEPC, such as gender, multifetal pregnancies, gestational age at birth, maternal and obstetric complications (vaginal bleeding, preeclamptic toxemia and hypertension, polyhydramnion, oligohydramnion), fetal infections, IUGR, asphyxia, malformations and chromosomal aberrations, mode of diagnosis (postmortem, ultrasound or both), and long-term outcome. We also summarized the morphologic characteristics of CSEPC, such as laterality, location, size, and ultrasound results during follow-up of CSEPC.

However, in order to obtain a meaningful comparison of the incidence rates of the examined variables between CSEPC cases

NICU = neonatal intensive care unit
IUGR = intrauterine growth restriction

and the general neonatal population, we performed a *targeted* meta-analysis of only 120 CSEPC cases described in 9 of the 24 reports (8,9,10,15,16,17,22,23, and our cases). We selected these nine reports for the *targeted* meta-analysis for several reasons: a) they were published more recently (1983–97), b) they consist of relatively large numbers (210–4,000) of screened neonates, and c) diagnosis of CSEPC was made by head ultrasound. Of these nine reports, five were prospective studies. The screened populations differed in the various reports. In six reports, all babies admitted to the NICU were screened by head ultrasound, while in the other three, only premature babies – all newborns or healthy term neonates – were screened. Through the *targeted* meta-analysis we also tried to identify the variables that might predict a higher risk for an unfavorable outcome.

Statistical analysis of data

Because of the small numbers of CSEPC cases in each of the 24 reports (1–25 cases each), we found meta-analysis to be the optimal statistical method for analyzing the data and creating a single pooled estimate for each variable tested [24,25]. Statistical comparisons and conclusions regarding associated variables and outcome of CSEPC were drawn from the *targeted* meta-analysis.

Pooled incidence rates for each variable were computed using the weighted average incidence rates for individual reports. A comparison of the incidence of specific variables between the CSEPC group and the general maternal/neonatal population group (known standards from acknowledged textbooks of Neonatology and Perinatal Medicine [26–39]) was performed using the one-sided *Z*-test. It was impossible to compare the incidence of the various variables between the CSEPC group and the population of the screened babies in whom CSEPC were not detected because of lack of adequate data on these babies in the reports. We opted to compare the incidence of the various risk factors to the incidence in the general population and not to that in the NICU sub-population because of lack of data on some of the variables in this sub-population. For outcome analysis, Chi-squared test and Fisher's exact test were utilized to assess whether the risk for an unfavorable outcome (mortality or neurodevelopmental handicap) was associated with any of the specific variables (e.g., prematurity versus birth at term). A *P* value of less than 0.05 was considered statistically significant.

Results

Our data

Table 1 summarizes data available on the 10 infants with CSEPC born in the Rambam Medical Center. Some of the neonates presented perinatal complications, such as prematurity, multifetal pregnancy, IUGR, preeclamptic toxemia in the mother, congenital CMV infection and congenital malformations. In most cases CSEPC were bilateral and located in the head of caudate nucleus or caudothalamic groove. There were no deaths, but two patients had hearing loss and four showed neurodevelopmental handicap during follow-up. Sonographic follow-up demonstrated resolution of CSEPC in 7 of our 10 cases.

Meta-analysis of the literature of CSEPC

Table 2 lists the conditions that were significantly more frequent in the CSEPC group compared to the general maternal/newborn population, as derived from the *targeted* meta-analysis. These conditions include the following: prematurity, maternal vaginal bleeding, preeclamptic toxemia, IUGR, asphyxia, fetal CMV and rubella infections, congenital malformations, chromosomal aberrations, infant mortality, and long-term neurological handicap. CSEPC were not found to be

CMV = cytomegalovirus

Table 1. Perinatal data, ultrasonographic findings and outcome in 10 neonates with CSEPC in the Rambam Medical Center

Case no.	Gender	Gestational age (wk)	Birth weight (g)	PET	IUGR	Congenital viral infection	Congenital malformations	Laterality of CSEPC	US location of CSEPC	Neurodevelopmental outcome*	Age at evaluation (mo)
1	M	41	3,395	–	–	CMV	–	Bilateral	HCN	Hearing loss, MDR	16
2	M	37	2,080	+	+	–	–	Bilateral	HCN, CTG	Normal	18
3	M	38	2,780	–	–	–	–	Unilateral	HCN	Normal	18
4	F	36	1,907	+	+	–	–	Bilateral	HCN	Normal	8
5	F	41	3,260	–	–	CMV	–	Bilateral	CTG	MDR	18
6	M	35	2,125	–	–	CMV	–	Bilateral	CTG	Hearing loss, MDR	18
7	M	37	4,300	–	–	–	–	Bilateral	HCN, TCN	Normal	7
8	F	37	2,780	–	–	–	–	Unilateral	HCN	Normal	6
9	M	32	1,155	+	+	–	VSD, hypospadias, hydrocephalus	Unilateral	Superior, external to lat. ventricle	MDR	8
10	M	35	1,805	+	+	CMV	–	Bilateral	CTG	Normal	2

* Developmental assessment by Gesell.

Follow-up by head ultrasonography showed resolution in 7 of 10 cases (CSEPC persisted in cases 1, 6 and 9).

PET = preeclamptic toxemia, HCN = head of caudate nucleus, CTG = caudothalamic groove, TCN = tail of caudate nucleus, VSD = ventricular septal defect, MDR = motor and developmental retardation.

significantly associated with gender, multifetal pregnancy or amniotic fluid abnormalities.

Through our *comprehensive* summary, we found that 77.6% of CSEPC cases were diagnosed by ultrasonography and CSEPC size was 2–11 mm [7,9,10,17–20,23]. CSEPC were bilateral in 48.8% of cases and resolved during ultrasound follow-up in 93.5% of cases between 1 and 12 months of age. CSEPC were located in the caudothalamic groove, frontal horn, and head of caudate nucleus in 39.1%, 22.4% and 14.3% of cases, respectively. In the remaining 24.2% of cases CSEPC were located in other subependymal areas.

Table 3 shows the possible risk factors for an unfavorable outcome (mortality or neurodevelopmental handicap), as derived from the *targeted* meta-analysis. Owing to the small numbers of cases of CSEPC presenting certain perinatal conditions or certain morphologic features and due to missing information on the outcome in some cases, we could not assess the effect of all conditions on outcome. However, we could evaluate the impact on unfavorable outcome in terms of neurodevelopmental handicap in CSEPC cases, of either the presence or absence of each of the following: prematurity, IUGR, fetal infections, congenital malformations and chromosomal aberrations, laterality of the CSEPC and resolution of CSEPC. We could not determine an association of any tested parameter with mortality in CSEPC cases because of the small numbers of infants with CSEPC who died.

Table 2. Targeted meta-analysis of CSEPC cases (9 reports, 120 cases): Incidence of perinatal factors, potential etiologies and unfavorable outcome in the CSEPC population compared to the general population

Variable	No. of reports: no. of cases (out of 9: out of 120)	No. of CSEPC cases with variable	Variables in CSEPC cases (%)	Variables in the general population (%) [Ref]	*P* <
Gender (male:female)	4:68	38:30	55.8:44.2		NS
Product of multi-fetal pregnancy	4:61	11	18.03	10–12 [27]	NS
Prematurity	9:120	53	44.16	8–10.7 [28]	0.0001
Complicated pregnancy					
Vaginal bleeding	1:25	3	12	3.8 [29]	0.032
PET and hypertension	5:50	11	22	5–10 [30]	0.005
Polyhydramnion	1:7	0	0	0.9 [31]	NS
Oligohydramnion	1:7	1	14.28	0.4–19 [32]	NS
IUGR	4:61	11	18	4–8 [33]	0.004
Asphyxia	3:37	7	18.91	1–1.5 [34]	0.0001
Fetal infections					
CMV	4:43	9	20.93	0.4–2.3 [35]	0.00001
Rubella	5:62	4	6.45	0.00004 [36]	0.00001
Toxoplasma, influenza, and others	3:42	3	7.14	No data	–
Congenital malformations*	5:72	21	29.16	1 [37]	0.00001
Chromosomal aberrations**	2:31	2	6.45	0.6 [38]	0.00001
Outcome					
Infant mortality	6 : 73	4	5.47	0.7–1 [39]	0.00001
Neurodevelopmental handicaps***	8 : 106	31	29.24	0.3–0.7 [40]	0.00001

P = value when comparing incidence between CSEPC cases and the general population.
* Mainly cerebral, cardiac, renal, urogenital, musculoskeletal anomalies, and anomalies associated with congenital rubella syndrome and CMV infection, Schinzel-Giedion syndrome and Zellweger syndrome.
** 22ph, 46XXdel(1), Hirschhorn-Wolf syndrome.
*** Mental retardation, psychomotor retardation, motor delay, cerebral palsy, different kinds of paralysis, hearing impairment.

There was no significantly increased risk for neurodevelopmental handicap in association with prematurity or bilateral CSEPC, as compared to birth at term or unilateral CSEPC, respectively. On the other hand, we found a significantly higher risk for neurodevelopmental handicap in CSEPC associated with IUGR, fetal infections, malformations and chromosomal aberrations, or unresolved CSEPC, as compared to no IUGR, no fetal infections, no congenital malformations or CSEPC resolution.

Through the *targeted* meta-analysis (based on 5 reports, 68 CSEPC cases), we could also assess the outcome in the absence of any of the above risk factors. For infants born without any of the following: IUGR, fetal infections or malformations and chromosomal aberrations, there was a 4.87% (2/41) risk for mortality (necrotizing enterocolitis in one infant and hypoxic ischemic encephalopathy in another) and a 4.87% (2/41) risk for neurodevelopmental handicap. The presence of one or more of these factors conferred a 63–88% risk for neurodevelopmental handicap.

Discussion

CSEPC is not an uncommon finding in neonates and should be sought during brain ultrasonographic examination. CSEPC are not detected by fetal ultrasound examinations, probably due to resolution limits of the fetal ultrasound and to the general unawareness of obstetricians to this entity. The results of this study provide information on CSEPC with regard to the etiological associations, morphologic characteristics and possible underlying conditions that influence outcome.

In spite of the recognized pitfalls associated with the method

Table 3. Risk factors for unfavorable outcome: *targeted* meta-analysis (120 patients, 9 reports)

Variable	No. of patients (no. of reports)	Mortality (% patients)*	Neurodevelopmental handicap Patients (%)	*P* value**
Prematurity	105 (8)			
Yes	46	4.34	36.95	NS
No	59	3.38	25.42	
IUGR	49 (3)			
Yes	9	0	88.88	< 0.002
No	40	2.5	30	
Fetal infection* **	82 (6)			
Yes	15	0	66.6	< 0.005
No	67	2.98	16.41	
Malformations & chromosomal aberrations	68 (5)			
Yes	19	10.52	63.15	< 0.001
No	49	2.04	20.4	
Head US findings	72 (6)			
Unilateral CSEPC	36	5.55	47.22	NS
Bilateral CSEPC	36	5.55	38.88	
US follow-up	54 (3)			
CSEPC not resolved	11	9.09	90.9	< 0.005
CSEPC resolved	43	0	25.58	

* Numbers too small for statistical evaluation.
** Chi-squared test or Fischer's exact test.
*** CMV, rubella, influenza, toxoplasmosis and others.
US = ultrasound

of meta-analysis, the summation of series of patients from appropriate reports relevant to a specific issue in a reasonable total analyzable number of cases is indispensable for performing an appropriate statistical analysis and obtaining judicious conclusions [24,25]. One of the drawbacks of the present meta-analysis was the heterogeneity of the populations screened in the various reports, including the nine reports used in the *targeted* meta-analysis. Therefore, the comparison of the incidence rates of the various conditions between the CSEPC population and the general neonatal population should be considered with caution. However, the comparison within the CSEPC population of the rate of neurodevelopmental handicap, between cases with or without various risk factors, is valid. Another drawback is a possible under-diagnosis at birth of prenatal infarcted/injured areas of the germinal matrix, since only areas that already cavitated *in utero* are displayed by ultrasound as CSEPC.

The *targeted* meta-analysis demonstrated a significant association between CSEPC and prematurity, probably because of underlying conditions in the fetus that cause CSEPC and also induce premature labor. In addition, CSEPC was significantly associated with obstetric complications such as vaginal bleeding, preeclamptic toxemia, IUGR and asphyxia, which are conditions that might be associated with a reduced perfusion to the developing fetal brain and might thus contribute to the creation of CSEPC. Fetal infections, mainly CMV and rubella, usually cause a generalized viral disease in the fetus involving the brain and the subependymal area, and could lead to CSEPC [1–3,11]. The strong association between CSEPC and chromosomal aberrations or congenital malformations could be explained by the multi-organ fetal derangements in these conditions, often involving the vulnerable subependymal area.

CSEPC are bilateral in about half the cases and can occur in any periventricular subependymal area, with a predilection to the caudothalamic groove. Local hemorrhage, infarction and post-viral local germinolysis are known to affect the fetal periventricular zone [4] and may be considered as pathogenic factors of CSEPC. Ultrasonographic follow-up shows that most CSEPC disappear, but the mechanism of resolution of CSEPC is not clear. Since CSEPC contents might be partially or completely absorbed, their size becomes too small to be detected by ultrasound during follow-up.

The higher risk for neurodevelopmental handicap whenever CSEPC are associated with IUGR, chromosomal aberrations, malformations or fetal infections, might be due to the overall high injurious potential inherent in these underlying conditions in the fetus. In addition, persistence of CSEPC during ultrasonographic follow-up carries a higher risk for neurodevelopmental handicap. It could be speculated that CSEPC resolution by ultrasound might occur more often when CSEPC are originally smaller in size, probably reflecting decreased severity of the underlying condition.

It appears that the mere presence of CSEPC in cases with the above-mentioned adverse fetal conditions does not increase the risk for an unfavorable outcome, since absence of any of these fetal conditions in neonates with CSEPC indicates a good prognosis. In these cases one can assume that CSEPC resulted from an infarction or hemorrhage that has meanwhile resolved. The outcome in these cases depends on how many neurons were lost and on the plasticity of the fetal brain.

When confronted with a newborn baby with CSEPC, the neonatologist is advised to look for certain perinatal complications as possible etiological factors for CSEPC, which could also help in predicting an unfavorable outcome. On these grounds, the physician will also be able to provide parents with reliable information regarding prognosis. Babies with CSEPC should remain in follow-up for evaluation of their neurodevelopmental status, in view of the basic conditions that are associated with CSEPC. Repeat head ultrasonography is also advisable in order to observe the possible resolution of the pseudocysts.

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You should never have your best trousers on when you go out to fight for freedom and truth

Henrik Ibsen, Norwegian playwright (1828–1906)