Outcome of Fetuses with Supratentorial Extra-Axial Intracranial Cysts: A Systematic Review

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Key Words
Fetal intracranial cysts · Extra-axial supratentorial cysts · Ultrasound · Cavum veli interpositi · Arachnoid cysts

Abstract
Objective: To investigate the incidence of associated anomalies, aneuploidy, cyst progression, need for surgery and neurodevelopmental outcome in fetuses with extra-axial supratentorial intracranial cysts.

Data Sources: MEDLINE, Embase and CINAHL databases were searched and the following outcomes analyzed: associated central nervous system (CNS) and extra-CNS anomalies detected at the scan, chromosomal anomalies, additional CNS anomalies detected only at prenatal MRI, additional CNS anomalies detected only after birth, cyst progression in utero, neurological outcome and need for surgery. Two authors reviewed all abstracts independently. Results were reported as proportions, and between-study heterogeneity was explored using the I² statistic; fixed or random effect models were used accordingly. Results: Ten studies involving 47 fetuses were included in the meta-analysis. Arachnoid cysts (n = 24) had associated CNS anomalies and extra-CNS in 73% (95% CI 56–88) and 14% (95% CI 4–29), respectively. The most common associated anomalies were ventriculomegaly and callosal abnormalities. Chromosomal abnormalities were present in 6% (95% CI 0–30), but fetuses with isolated cysts were always euploid (0/7; 95% CI 0–29). Fetal MRI and postnatal examination identified 5 additional cases (21%, 95% CI 1–57). Cavum veli interpositi (CVI) cysts had associated CNS and extra-CNS anomalies in 31% (95% CI 13–52) and 6% (95% CI 0–29), respectively. No chromosomal or callosal anomalies were found in these cases. In isolated CVI cysts, no cases of associated anomalies were detected postnatally. Intrauterine regression occurred in 23% of CVI cysts and in none of the arachnoid cysts. In children with arachnoid cyst, the occurrence of hydrocephaly and mass effect on the adjacent structures were observed in 23.9% (95% CI 8.3–4.4) and 26.8% (95% CI 4.0–60.1), respectively. None of the cases included had abnormal motor outcome or intelligence. The rate of surgery was 34.7% (95% CI 16.0–56.4). None of the children with a prenatal diagnosis of isolated CVI cyst experienced any of the adverse outcomes explored in this review.

Conclusions: Extra-axial supratentorial cysts diagnosed in utero are
frequently associated with other neural and extra-neural anomalies. However, this may represent the consequence of a selection bias. Interhemispheric arachnoid cysts were typically associated with callosal anomalies. Abnormal karyotypes were seen only in fetuses with multiple anomalies. Arachnoid, but not CVI, cysts frequently increased in size throughout gestation.

Introduction

Fetal intracranial cysts are relatively common on prenatal ultrasound assessment. Intracranial cysts are commonly classified as intraventricular, intraparenchymal and extra-axial [1]. Extra-axial cysts are frequently the consequence of entrapped fluid within the layers of the arachnoid membrane. Although histological confirmation is usually lacking, because most of these cysts are not surgically removed, the term ‘arachnoid cyst’ is commonly used to indicate any extra-axial cyst, particularly in the obstetric literature. The most frequent locations include the surface of the cerebral hemispheres in the sites of major fissures, the region of sella turcica, the anterior fossa and the middle fossa [2]. Less frequently, they are seen in the posterior fossa. Cysts located in proximity of the splenium of the corpus callosum are commonly referred to as cavum veli interpositi (CVI) cysts and probably have a different etiology from cysts in other locations.

Counseling women carrying fetuses with a prenatal diagnosis of intracranial extra-axial cysts is challenging. The current evidence is sparse and mainly deriving from postnatal literature. Hydrocephaly, symptoms related to the compression of the cyst on the adjacent structures, abnormal motor and developmental outcomes have been frequently reported to be associated with these conditions. Furthermore, there are limited numerical data about the association with other anomalies and chromosomal aberrations. The presence of associated anomalies, cyst location and size have been reported to be the main determinants in predicting the outcome after birth. However, postnatal series are likely to be biased as only symptomatic patients are reported, thus probably representing the most extreme end of the spectrum, not taking into account asymptomatic individuals with isolated, probably undiagnosed intracranial cysts.

The aim of this systematic review was to ascertain the perinatal and neurodevelopmental outcome of fetuses with isolated intracranial cysts diagnosed prenatally.

Data Sources

Protocol, Eligibility Criteria, Information Sources and Search

This review was performed according to an a priori-designed protocol and recommended for systematic reviews and meta-analysis [3–5]. MEDLINE, Embase and CINAHL were searched electronically on January 2014, utilizing combinations of the relevant medical subject heading (MeSH) terms, key words and word variants for ‘intracranial cysts’ and ‘outcome’ (online suppl. material 1; see www.karger.com/doi/10.1159/000445718 for all online suppl. material). The search was updated in January 2015. The search and selection criteria were restricted to the English language. Reference lists of relevant articles and reviews were hand searched for additional reports. The PRISMA guidelines were followed [6].

Study Selection, Data Collection and Data Items

Studies were assessed according to the following criteria: population, outcome, gestational age at examination, type of imaging assessment and location of the cyst. Two authors (A.Y., F.D.) reviewed all the abstracts independently. Agreement about potential relevance was reached by consensus, and full text copies of those papers were obtained. Two reviewers (A.Y., F.D.) independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed by the reviewers and consensus reached. If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. For those articles in which the relevant information was not reported but the methodology was such that this information would have been recorded initially, the authors were contacted.

We used the term supratentorial arachnoid cyst to indicate all extra-axial cysts with the exception of those occurring in the proximity of the splenium of the corpus callosum, which were considered separately (CVI cysts). The rationale behind the distinction between arachnoid and CVI cysts is the consistent association of the latter in the literature, when isolated, with normal outcome. In fact, it is still unknown whether to consider isolated CVI cysts as a normal variant. Therefore, we assumed that analyzing CVI cysts with other supratentorial cysts may falsely give reassuring data on the outcome of supratentorial extra-axial cysts. The following entities were excluded: infratentorial cysts and cyst-like structures in the posterior fossa; intraventricular cysts; intraparenchymal
cyst; cystic malformations of vascular nature, such as vein of Galen aneurysm or dural sinuses anomaly. In addition, we excluded postnatal studies or studies from which cases diagnosed prenatally could not be extracted, autopsy-based studies, studies reporting concordance between pre- and postnatal diagnosis of intracranial cysts (unless they provided information about the location of the cyst and whether the cyst was isolated or not), and cases with a lack of a clear definition of the anomaly. Finally, series that reported cysts only in association with a given anomaly were excluded.

The incidences of the following perinatal outcomes were analyzed in fetuses with extra-axial supratentorial intracranial cysts:

1. Associated major structural central nervous system (CNS) and extra-CNS anomalies
2. Chromosomal abnormalities
3. Additional major CNS anomalies detected only at prenatal magnetic resonance imaging (MRI) but missed at the ultrasound scan
4. Additional CNS and extra-CNS major anomalies detected only at postnatal imaging or clinical evaluation but missed at prenatal imaging
5. Progression of the cyst in utero
6. Occurrence of hydrocephaly
7. Mass effect of the cyst on the adjacent structures
8. Need for surgery
9. Neurodevelopmental outcomes; including abnormal motor outcome and developmental delay

The occurrence of CNS and extra-CNS malformations was calculated in all fetuses with a prenatal diagnosis of supratentorial cysts. The incidence of abnormal karyotype was assessed both in fetuses with associated structural anomalies and in those with isolated cysts, defined as cysts with no associated structural CNS and extra-CNS anomalies detected at the prenatal ultrasound scan. Only cases who had their full karyotype tested either pre- or postnatally were included. The presence of additional anomalies detected only at pre- and postnatal MRI was assessed only in fetuses with no additional anomalies detected at the scan and at prenatal imaging, respectively. Furthermore, the assessment of the progression of the cystic mass in utero was explored only in fetuses without associated structural anomalies. As ventriculomegaly is a frequent finding in cases of intracranial cysts – often related to cerebrospinal fluid dynamic changes secondary to the mass effect of the cystic mass – the incidence of associated anomalies was calculated twice, once considering ventriculomegaly as an associated anomaly and once not considering it as such.

Hydrocephaly was defined as an enlargement of the ventricular cavities associated with signs of intracranial hypertension. Mass effect of the cyst on the adjacent structures was defined as a compression of the cyst causing clinical symptoms. Abnormal motor outcome and intelligence were ascertained only in studies where an objective tool for the neurodevelopmental performance was adopted.

The occurrence of an abnormal neurodevelopmental outcome was assessed only in cases with isolated intracranial cysts, defined as cysts without associated intra- and extracranial anomalies diagnosed prenatally and confirmed at birth and in arachnoid and CVI cysts separately. For the purpose of this analysis, ventriculomegaly was not considered an associated anomaly.

Only full-text articles were considered eligible for the inclusion. Case reports, conference abstracts and case series with fewer than two were also excluded in order to avoid publication bias.

Risk of Bias, Summary Measures and Synthesis of the Results

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for cohort studies. According to the NOS, each study is judged on three broad perspectives: selection of the study groups, comparability of the groups and ascertainment of the outcome of interest [7]. Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure and the demonstration that the outcome of interest was not present at the start of the study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts based on the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, length and adequacy of follow-up [7]. According to the NOS, a study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability. Criteria for quality assessment using the NOS are reported in online supplementary table 2.

We used meta-analyses of proportions to combine data [8, 9]. Funnel plots displaying the outcome rate from individual studies versus their precision (1/standard error) were carried out with an exploratory aim. Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was <10. In this case, the power of the tests is too low to dis-
tistinguish chance from real asymmetry [10]. Between-study heterogeneity was explored using the I² statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, whereas I² values of ≥50% indicate a substantial level of heterogeneity. A fixed effects model was used if substantial statistical heterogeneity was not present. In contrast, if there was evidence of significant heterogeneity between studies included, a random effect model was used. All proportion meta-analyses were carried out using StatsDirect 2.7.9 (StatsDirect Ltd, Altrincham) and MetaDisc v1.4 (www.hrc.es/investigacion/metadisc_en.htm).

Results

Study Selection and Characteristics
A total of 523 articles were identified, of which 107 were assessed with respect to their eligibility for inclusion (online suppl. table 3). Ten studies were included in the systematic review (fig. 1) [11–20]. These 10 studies included 47 fetuses with extra-axial supratentorial intracranial cysts. The general characteristics of the studies included in the systematic review are reported in table 1. Quality assessment of the included studies performed using the NOS for cohort studies is shown in table 2. Almost all the included studies showed an overall good rate with regard to the selection and comparability of the study groups and for the ascertainment of the outcome of interest. The main weaknesses of these studies were represented by their small sample sizes, being series from high-risk populations, and lack of ascertainment of the individual outcomes. Furthermore, most studies had a relatively short period of follow-up after birth and included different neurodevelopmental tools.

Synthesis of the Results
The pooled proportions of the outcomes explored in this systematic review were as follows (table 3; fig. 2–7).
Arachnoid Cysts

The overall incidence of associated CNS anomalies and extra-CNS anomalies in the 24 fetuses with a prenatal diagnosis of arachnoid cyst were 74% (95% CI 56–88) and 14% (95% CI 3–29), respectively. The most frequent neural malformations were ventriculomegaly (62%, 95% CI 44–79) and abnormalities of the corpus callosum (40%, 95% CI 23–58), exclusively seen with interhemispheric cysts. When ventriculomegaly was excluded from the analysis, the incidence of additional CNS anomalies was lower (31%, 95% CI 15–50). Chromosomal abnormalities occurred in 1 of 15 cases (6%, 95% CI 0–30), but none were found in the 7 isolated cases (pooled prevalence: 0%, 95% CI 0–29).

There were 2 cases of associated anomalies detected only at fetal MRI and missed at the scan, both in the form of callosal abnormalities. These anomalies, detected only...
There were 2 additional anomalies detected only at postnatal imaging or clinical examination (21%, 95% CI 1–57), consisting of agenesis of the corpus callosum (ACC) in one case, and ACC and intracranial teratoma in another case. An increase in the size of the cyst in utero was reported in 22% (95% CI 11–36) of the cases, while none of the cases included in the analysis showed a significant reduction in the cyst size in utero.

Five studies (15 fetuses) explored the occurrence of hydrocephaly in children with a prenatal diagnosis of iso-

### Table 3. Pooled proportions for the outcomes observed in this systematic review

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies, n</th>
<th>Fetuses, n/N</th>
<th>Raw % (95% CI)</th>
<th>Pooled proportiona (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated CNS anomalies (all cysts)</td>
<td>9</td>
<td>22/38</td>
<td>57.9 (40.8–73.7)</td>
<td>53.0 (34.2–71.4)</td>
</tr>
<tr>
<td>Arachnoid cysts only</td>
<td>6</td>
<td>17/22</td>
<td>77.3 (54.6–91.2)</td>
<td>73.7 (56.2–88.0)</td>
</tr>
<tr>
<td>CVI cysts only</td>
<td>4</td>
<td>5/16</td>
<td>31.3 (11.0–58.7)</td>
<td>31.1 (13.2–52.5)</td>
</tr>
<tr>
<td>Associated extra-CNS anomalies (all cysts)</td>
<td>9</td>
<td>3/38</td>
<td>7.9 (1.7–21.4)</td>
<td>12.5 (4.7–23.3)</td>
</tr>
<tr>
<td>Arachnoid cysts only</td>
<td>6</td>
<td>2/22</td>
<td>9.1 (1.1–29.2)</td>
<td>14.1 (3.9–29.1)</td>
</tr>
<tr>
<td>CVI cysts only</td>
<td>4</td>
<td>1/16</td>
<td>6.3 (0.2–30.2)</td>
<td>5.9 (0.1–28.7)</td>
</tr>
<tr>
<td>Chromosomal abnormalities (all cysts)</td>
<td>9</td>
<td>2/19</td>
<td>10.5 (1.3–33.2)</td>
<td>16.8 (5.5–32.5)</td>
</tr>
<tr>
<td>Arachnoid cysts only</td>
<td>6</td>
<td>1/15</td>
<td>6.7 (1.7–31.9)</td>
<td>6.3 (0.1–30.2)</td>
</tr>
<tr>
<td>CVI cysts only</td>
<td>3</td>
<td>1/4</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Chromosomal abnormalities (isolated cysts)</td>
<td>7</td>
<td>0/10</td>
<td>0.0 (0.0–30.8)</td>
<td>0.0 (0.0–30.8)</td>
</tr>
<tr>
<td>Arachnoid cysts only</td>
<td>4</td>
<td>0/7</td>
<td>0.0 (0.0–41.0)</td>
<td>0.0 (0.0–28.5)</td>
</tr>
<tr>
<td>CVI cysts only</td>
<td>3</td>
<td>0/3</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Additional anomalies detected only at prenatal MRI</td>
<td>4</td>
<td>2/7</td>
<td>28.6 (3.7–71.0)</td>
<td>33.2 (5.0–71.0)</td>
</tr>
<tr>
<td>Arachnoid cysts only</td>
<td>2</td>
<td>2/3</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>CVI cysts only</td>
<td>2</td>
<td>0/4</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Associated anomalies detected only postnatally</td>
<td>9</td>
<td>4/34</td>
<td>11.8 (3.3–27.5)</td>
<td>13.1 (4.8–24.7)</td>
</tr>
<tr>
<td>Arachnoid cysts only</td>
<td>6</td>
<td>3/18</td>
<td>16.7 (3.6–41.4)</td>
<td>21.2 (1.0–57.3)</td>
</tr>
<tr>
<td>CVI cysts only</td>
<td>4</td>
<td>0/15</td>
<td>0.0 (0.0–21.8)</td>
<td>0.0 (0.0–21.8)</td>
</tr>
<tr>
<td>Progression of the cyst in uterus</td>
<td>9</td>
<td>6/31</td>
<td>19.4 (7.5–37.5)</td>
<td>21.9 (10.5–36.2)</td>
</tr>
<tr>
<td>Arachnoid cysts only</td>
<td>5</td>
<td>4/16</td>
<td>25.0 (7.3–52.4)</td>
<td>28.3 (11.6–48.9)</td>
</tr>
<tr>
<td>CVI cysts only</td>
<td>4</td>
<td>2/15</td>
<td>13.3 (1.7–40.5)</td>
<td>16.6 (2.3–40.2)</td>
</tr>
<tr>
<td>Hydrocephaly</td>
<td>5</td>
<td>3/15</td>
<td>20.0 (4.3–48.1)</td>
<td>23.87 (8.3–4.4)</td>
</tr>
<tr>
<td>Arachnoid cysts only</td>
<td>4</td>
<td>0/16</td>
<td>0 (0–20.6)</td>
<td>0 (0–20.6)</td>
</tr>
<tr>
<td>CVI cysts only</td>
<td>5</td>
<td>0/15</td>
<td>0 (0–20.6)</td>
<td>0 (0–20.6)</td>
</tr>
<tr>
<td>Mass effect</td>
<td>5</td>
<td>3/15</td>
<td>20.0 (4.3–48.1)</td>
<td>26.84 (4.0–60.1)</td>
</tr>
<tr>
<td>Arachnoid cysts only</td>
<td>4</td>
<td>0/15</td>
<td>0 (0–20.6)</td>
<td>0 (0–20.6)</td>
</tr>
<tr>
<td>CVI cysts only</td>
<td>5</td>
<td>0/11</td>
<td>0 (0–28.5)</td>
<td>0 (0–28.5)</td>
</tr>
<tr>
<td>Intelligence/developmental delay</td>
<td>2</td>
<td>0/9</td>
<td>0 (0–33.6)</td>
<td>0 (0–33.6)</td>
</tr>
<tr>
<td>Arachnoid cysts only</td>
<td>2</td>
<td>0/9</td>
<td>0 (0–33.6)</td>
<td>0 (0–33.6)</td>
</tr>
<tr>
<td>Motor disorders</td>
<td>5</td>
<td>0/15</td>
<td>0 (0–21.8)</td>
<td>0 (0–20.6)</td>
</tr>
<tr>
<td>Arachnoid cysts only</td>
<td>4</td>
<td>0/16</td>
<td>0 (0–20.6)</td>
<td>0 (0–20.6)</td>
</tr>
<tr>
<td>Need for surgery</td>
<td>5</td>
<td>5/15</td>
<td>33.33 (11.8–61.6)</td>
<td>34.73 (16.0–56.4)</td>
</tr>
<tr>
<td>Arachnoid cysts only</td>
<td>4</td>
<td>0/16</td>
<td>0 (0–20.6)</td>
<td>0 (0–20.6)</td>
</tr>
<tr>
<td>CVI cysts only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Using StatsDirect. b Using Meta-Disc. NC = Noncomputable (less than five observations overall).

at fetal MRI and missed at the scan, were too few to allow a comprehensive meta-analytic approach.
lated supratentorial arachnoid cyst reporting an overall rate of 23.9% (95% CI 8.3–4.4; table 3). The presence of the cyst was responsible for an overt mass effect on the adjacent structures in 26.8% (95% CI 4.0–60.1) of the cases, while in none of the cases included was abnormal motor outcome or intelligence reported. The rate of surgery in fetuses with isolated arachnoid cyst due to the presence of symptoms or enlargement of the cystic mass was 34.7% (95% CI 16.0–56.4).

CVI Cysts

There were 23 fetuses with a prenatal diagnosis of CVI cyst identified in the literature. The overall incidence of associated CNS anomalies and extra-CNS anomalies in fetuses with a prenatal diagnosis of CVI cyst was 5/16 (31%, 95% CI 13–53) and 1/16 (6%, 95% CI 0–29), respectively. Ventriculomegaly was reported in 15% (95% CI 3–33). When ventriculomegaly was excluded, the overall rate of additional CNS anomalies in the CVI cyst was 21% (95% CI 7–41). No callosal abnormalities were reported.

Although the rate of chromosomal abnormalities could not be computed in either overall or isolated CVI due to the limited number of cases, all the fetuses tested (6/6) were euploid.

When isolated, there were no cases of associated anomalies detected postnatally. The in utero progression of the cyst occurred in 2/15 cases (17%, 95% CI 2–40), while the in utero regression of the cyst size occurred in 23% (95% CI 8–45) of the cases.

Four studies (16 fetuses) explored the outcome of children with a prenatal diagnosis of CVI cyst. Although the included studies reported different periods of follow-up, none of the children with a prenatal diagnosis of isolated CVI cyst experienced any of the adverse outcomes explored in this systematic review (table 3).

The Kaplan-Meier analysis of children with a prenatal diagnosis of infratentorial intracranial cysts is shown in figure 8. The likelihood of having any of the symptoms related to the presence of the cyst was significantly different in children with a prenatal diagnosis of isolated arachnoid compared to CVI cyst (p = 0.008). Children with a prenatal diagnosis of isolated arachnoid cyst were more likely to experience symptoms or having surgery in the first 25 months of life, while the occurrence of symptoms was relatively unlikely after this time.
Discussion

Summary of Evidence

Extra-axial supratentorial cysts are rare anomalies. This exhaustive literature search identified only 47 cases which fulfilled our inclusion criteria. Therefore, it is difficult to extrapolate precise indications for the workup and management of these conditions. Associated anomalies were frequently encountered, and the most common were ventriculomegaly and partial or complete ACC. The latter was only seen with arachnoid interhemispheric cysts, and the association appears to be clinically relevant as it has been reported to carry prognostic implications [21]. The high number of associated abnormalities may suggest that there is a degree of selection bias in the reported studies. Chromosomal aberrations were limited to cases with multiple anomalies detected on prenatal ultrasound scan. Fetal MRI was useful in the diagnostic workup in at least 2 cases, where callosal abnormalities that had escaped sonographic detection were found. CVI cyst demonstrated a progression in 16% of cases, but more frequently regressed.

Fig. 6. Pooled proportion for the occurrence of symptoms and abnormal neurodevelopmental outcomes in children with a prenatal diagnosis of isolated supratentorial arachnoid cyst.
There were some associated anomalies undetected by antenatal imaging in the group of arachnoid cysts. However, this was most likely the consequence of incomplete ascertainment in old studies as in 2 out of 3, ACC was present, an anomaly that is very precisely recognized since early gestation with current prenatal imaging techniques. There were no reports of missed anomalies in the cases with CVI cysts. Children with a prenatal diagnosis of supratentorial arachnoid cysts experience symptoms related to the presence of the cyst in almost a quarter and need surgery in approximately one third of the cases. When present, symptoms are more likely to occur within the first 2 years of life. Conversely, CVI cysts may be considered benign conditions and the occurrence of adverse neurodevelopmental outcome negligible.

Fig. 7. Pooled proportion for the occurrence of symptoms and abnormal neurodevelopmental outcomes in children with a prenatal diagnosis of isolated CVI cyst.

Fig. 8. Kaplan-Meier curve showing the occurrence of symptoms due to the presence of an intracranial supratentorial cyst over time.
**Limitations**

The main limitation of this systematic review was the small number of studies, which did not permit meaningful stratified meta-analyses to explore the test performance in the subgroups of patients that may be less or more susceptible to bias. The assessment of the potential publication bias was also problematic, both because of the nature of the outcome (rates with the left side limited to the value zero), which limits the reliability of funnel plots, and because of the scarce number of individual studies, which strongly limits the reliability of formal tests. Furthermore, all the studies included were retrospective, thus liable to a considerable risk of selection bias. In addition, several outcomes and associations were not adequately reported in many studies. An example is the additional findings on prenatal MRI, which were reported only in 2 studies. Another limitation is the inability to differentiate outcome by location (e.g. midline vs. peripheral). This is mainly due to the low overall number of cases included. Furthermore, due to the relatively short postnatal follow-up period, the overall rate of additional anomalies detected only after birth and missed prenatally may have been underestimated.

The size and location of the cyst are the major determinants in predicting the rate and the type of symptoms related to the presence of the cyst. However, in view of the very small number of cases included, such a subanalysis was not carried out. Therefore, it might be possible that the estimated proportion of abnormal neurodevelopmental outcome reported in this review might have overestimated the actual burden of disabilities associated with these anomalies. Patients with large cysts are more likely to have symptoms and undergo surgery. Furthermore, several outcomes and associations were not adequately reported in many studies. Finally, the heterogeneity in the neurodevelopmental tool used to ascertain the neurocognitive performance of these children and the variability in the time of follow-up might have significantly influenced the figures reported in the current review. Despite these limitations, this review represents the best estimate of the adverse outcome associated with this prenatal diagnosis.

**Implications for Clinical Practice and Future Perspectives**

The results of our review may be of help to the clinicians in the diagnostic workup, parental counseling and management of fetal intracranial supratentorial cysts. However, we do acknowledge that the overall number of collected cases is small. Arachnoid cysts have been reported to be associated with other anomalies including ACC, absent septum pellucidum, deficient cerebellar lobulation, Arnold-Chiari type I malformation, malformations of cortical developments, arteriovenous malformation, tetralogy of Fallot and sacrococcygeal tumor [1, 19, 22, 23]. We have found a strong correlation between interhemispheric arachnoid cysts and callosal abnormalities, and therefore we suggest that once such a cyst is encountered, a thorough ultrasound evaluation of the corpus callosum is mandatory. Conversely, CVI cysts were never associated with callosal anomalies. The limited number of cases does not allow to establish with certainty the role of antenatal MRI in such cases, but certainly this is indicated at least when the ultrasound examination is unsatisfactory. Ventriculomegaly was frequently seen with arachnoid cysts, and to a lesser extent with CVI cysts. In some cases, ventriculomegaly is probably secondary to a large cyst obstructing the cerebrospinal flow [2]. Indeed, many of the arachnoid cysts were described as large, and in 28% of cases they increased in size throughout gestation.

The cyst progression is thought to be the consequence of either a communication with the subarachnoid space with a ball valve mechanism or of cerebrospinal fluid production by a choroid plexus-like tissue contained within the cyst wall [2]. The cyst progression is an important determinant of the postnatal outcome as it increases the likelihood of the need for postnatal surgery. Parents should be informed that arachnoid cysts are likely to increase in size throughout gestation. Therefore, this is an indication for serial sonographic examinations in the third trimester. CVI cysts were less likely to increase in size (16.6% of cases) and regressed in 23% of cases. This observation supports the belief that in at least some cases these are normal variants. As CVI cysts are usually described as small, the association with ventriculomegaly that is occasionally seen is probably the consequence of a different mechanism from cerebrospinal fluid flow obstruction. The hypothesis that this association is the consequence of a referral bias is plausible. In the presence of primary ventriculomegaly, a more careful examination of the fetal brain is conducted, and this may result in a more frequent documentation of a CVI cyst.

Although the total number of cases was small, chromosomal aberrations were only seen with multiple anomalies. Therefore, the need of karyotyping fetuses with isolated cyst is uncertain. Finally, in the light of the present data, postnatal imaging should be arranged in

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order to confirm prenatal diagnosis and to rule out associated anomalies not detected during pregnancy, particularly in case of arachnoid cysts.

Ascertainment of neurocognitive status in congenital brain anomalies is challenging. Several factors such as the length of follow-up, the neurodevelopmental test adopted, the imaging tool used to confirm the diagnosis, the supportive neuropsychological therapies and the parental socioeconomic status are likely to influence the overall performance of a child affected by a congenital anomaly of the brain. Most of the studies exploring the neurodevelopmental status of children with intracranial cysts originate from pediatric case series. Postnatal studies are likely to be biased by the fact that the large majority of patients tested are referred because of symptoms, although the presence of intracranial cyst could be an incidental finding. Furthermore, most of the postnatal studies did not differentiate between the location of the cyst and the presence of associated cranial or extracranial anomalies.

Symptoms related to the presence of intracranial cyst do not always occur immediately after birth. The Kaplan-Meier analysis showed that, although the large majority of clinical symptoms are evident at birth, a significant proportion of children may exhibit signs due to compression of the cyst within 2 years of age; thus, a close follow-up is warranted in order to detect clinical symptoms amenable to treatment. The results of this review may be of help to the clinicians in the parental counseling and management of fetal intracranial supratentorial cysts. However, in view of the small sample size analyzed and different follow-up times, further studies are needed in order to precisely estimate the rate of abnormal neurocognitive status in children with a prenatal diagnosis of isolated intracranial cyst.

Conclusions

In fetuses with a prenatal diagnosis of an extra-axial supratentorial cyst, prenatal imaging should aim at ruling out associated anomalies and monitoring the cyst size and signs of compressions such as ventriculomegaly and macrocrania. Antenatal MRI may be used and is certainly indicated when the results of the ultrasound examination are not satisfactory. Chromosomal aberrations were seen only in fetuses with multiple anomalies.

The neurodevelopmental outcome of fetuses with isolated supratentorial arachnoid cysts is generally good, and the large majority of them do not require surgery. The occurrence of adverse outcome in children with isolated CVI is negligible. Large prospective studies with standardized protocols for diagnosis and management are needed in order to further ascertain the rate of abnormal neurodevelopmental outcome in children with a prenatal diagnosis of isolated intracranial cysts.

References


