Evaluation of intracranial cerebrospinal fluid cytology in staging pediatric medulloblastomas, supratentorial primitive neuroectodermal tumors, and ependymomas

Clinical article

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Object. The objective of this study was to determine the role of intracranial CSF examination in detecting true cases of early tumor dissemination. Cerebrospinal fluid dissemination is an ominous feature of pediatric brain tumors, occurring in as many as 30% of medulloblastomas, 25% of supratentorial primitive neuroectodermal tumors (PNETs), and 5% of ependymomas at diagnosis. Detecting early dissemination is important for determining both treatment and prognosis. Dissemination can be detected by evaluating imaging of the full neuraxis and by examining CSF cytology. Neuraxis MR imaging and lumbar CSF cytology evaluation are widely accepted methods for determining dissemination. However, the value of examining intracranial CSF cytology in detecting early dissemination is uncertain.

Methods. Under an institutional review board–approved protocol, medical records, pathology reports, and radiology reports for 150 patients who had undergone resection of brain tumors (88 with medulloblastomas, 21 with supratentorial PNETs, and 41 with ependymomas) and who had been evaluated using neuraxis MR imaging studies in the last 15 years were retrospectively reviewed. Radiology results were compared with the CSF cytology results and long-term disease outcomes.

Results. Between lumbar and intracranial CSF cytology results, 7 of 40 were discordant: in 2 intracranial CSF was negative and lumbar CSF was positive, and in 5 the reverse was true. The discordance percentage was 18%, with a kappa statistic of 0.36. Between MR imaging and lumbar CSF cytology results, 11 of 65 were discordant: in 9 the lumbar CSF was negative and MR imaging was positive, and in 2 the reverse was true. The discordance rate was 17%, with a kappa statistic of 0.27. Between MR imaging and intracranial CSF cytology results, 8 of 52 were discordant: in 3 intracranial CSF was negative and MR imaging was positive, and in 5 the reverse was true. The discordance rate was 15%, with a kappa statistic of 0.41. Patients with positive and negative results on perioperative neuraxis MR imaging studies had a median survival of 26.8 and 33.1 months, respectively (p = 0.02). Patients with positive and negative results on perioperative lumbar CSF cytology had a median survival of 20.1 and 31.4 months, respectively (p = 0.11). Patients with positive and negative results on intracranial CSF cytology had a median survival of 31 and 31.4 months, respectively (p = 0.84).

Conclusions. Discordance exists between the results of neuraxis MR imaging and lumbar and intracranial CSF cytology in perioperative detection of tumor dissemination for pediatric medulloblastoma, supratentorial PNETs, and ependymoma. In 1 case in this series, perioperative dissemination was detected by intracranial CSF cytology, but not by lumbar CSF cytology or neuraxis MR imaging. Isolated intracranial CSF cytology positivity may represent an earlier stage of disseminated disease. Complementary use of perioperative neuraxis MR imaging and lumbar and intracranial CSF cytology can reduce the incidence of missed diagnoses of dissemination. Survival analysis revealed that perioperative neuraxis MR imaging findings are correlated with survival, whereas perioperative lumbar and intracranial CSF cytology findings are not. (DOI: 10.3171/2010.5.PEDS09333)

Key Words • cerebrospinal fluid cytology • leptomeningeal dissemination • tumor staging • medulloblastoma • ependymoma • pediatric tumor

Abbreviations used in this paper: PNET = primitive neuroectodermal tumor; VP = ventriculoperitoneal.
the significant morbidities of such therapy in the pediatric population, an accurate assessment of extent of disease is needed. An ideal assessment will be maximally sensitive and specific for disseminated disease during the perioperative period, when oncological treatment plans are formulated.

Current diagnosis of disseminated disease is based on MR imaging of the neuraxis and sampling for CSF cytology. In the last 20 years there has been much discussion concerning the site of CSF sampling. It has been suggested in several studies that intracranial CSF is more sensitive than lumbar CSF.\textsuperscript{15,37} Other studies have suggested that the opposite is true.\textsuperscript{1} In most treatment protocols only lumbar CSF is evaluated. However, the aforementioned studies did not correlate CSF site analysis with the long-term patient outcomes. Furthermore, some of these studies analyzed adult patients and primary tumors that were both intracranial and extracranial in origin. Last, most studies analyzed CSF samples obtained during different periods in the disease progression. To assess the importance of CSF sampling sites in perioperative detection of disseminated disease, we conducted a retrospective study of a large pediatric population with a long-term assessment of disease status.

**Methods**

**Patient Group**

Under an institutional review board–approved protocol, we reviewed medical records, pathology reports, and radiology reports for 169 patients who had undergone resection of brain tumors between 1992 and 2007. One hundred fifty of these patients (88 with medulloblastoma, 21 with supratentorial PNETs, and 41 with ependymoma) had MR images of the neuraxis and were entered into the study. The study cohort consisted of 94 male and 56 female patients. At the time of initial tumor resection, the patient age ranged from 3.5 months to 23 years (mean 5.7 years). The pediatric nature of the patient population was established by virtue of their treatment at a children’s hospital. The time of follow-up ranged from 1.5 months to 14 years (mean 4 years). Twenty patients (13\%: 15 with medulloblastoma, 1 with supratentorial PNETs, and 4 with ependymoma) presented with disseminated disease demonstrated by MR imaging, and 20 more (14 with medulloblastoma, 5 with supratentorial PNETs, and 1 with ependymoma) progressed to disseminated disease on MR imaging studies obtained within 2 months to 2.9 years after surgery (mean 1 year). Forty-three patients (25 with medulloblastoma, 6 with supratentorial PNETs, and 12 with ependymoma) died, and 37 (18 with medulloblastoma, 5 with supratentorial PNETs, and 14 with ependymoma) were lost to follow-up before the 30-month mark. The group lost to follow-up did not significantly differ in demographic or tumor characteristics.

In terms of treatment, 141 patients received chemotherapy, radiation treatment, or both. Nine patients did not receive any adjuvant therapy. Fifty-five patients experienced local recurrences, 35 of whom died of the recurrence. Eight more patients died of postoperative or primary tumor complications. Due to differences in protocols in the last 15 years, not all patients underwent perioperative neuraxis MR imaging or lumbar and intracranial CSF cytology performed perioperatively, which was defined as within 1 month of the date of surgery. The intracranial CSF was harvested intraoperatively prior to tumor manipulation, or preoperatively through a ventricular catheter (in those children presenting with acute hydrocephalus). Available for analysis were 52 patients who had neuraxis MR imaging and intracranial CSF cytology, 65 who had neuraxis MR imaging and lumbar CSF cytology, and 40 who had intracranial and lumbar CSF cytology.

**Analysis of MR Imaging Studies**

Radiology reports were prepared by radiologists, and were considered positive for disseminated disease in the presence of either diffuse leptomeningeal enhancement or areas of focal enhancement.

**Analysis of CSF Cytology Studies**

The CSF cytology reports were prepared by staff pathologists for intracranial and lumbar CSF. Cytology results were considered positive when pathologists noted the presence of malignant cells.

**Statistical Analysis**

The concordance and discordance of results were calculated for each pair of detection methods. In the Kaplan-Meier survival analysis, probability values were calculated using the Gehan-Breslow-Wilcoxon test.

**Results**

**Lumbar Versus Intracranial CSF Cytology**

Forty patients had both lumbar and intracranial CSF cytology performed perioperatively. Five of 40 lumbar CSF samples and 8 of 40 intracranial CSF samples were positive for tumor cells. Three of 40 results were concordantly positive, and 30 of 40 were concordantly negative. Seven were discordant: in 2 cases intracranial CSF was negative and lumbar CSF was positive, and in 5 cases the reverse was true. The discordance percentage is 18\%, with a kappa statistic of 0.36. Of the 2 patients with positive lumbar CSF and negative intracranial CSF findings, 1 was treated clinically as having disseminated disease, and survived without recurrences for at least 9 years. The other patient was not treated clinically as if the disease was disseminated, and that individual died of progressive local disease in 4 months. Of the 5 patients with negative lumbar and positive intracranial CSF findings, 2 were treated as if the disease was not disseminated clinically, and both survived without recurrence. The other 3 were treated clinically as having dissemination, and 2 of them died of disseminated disease, whereas 1 remains free of dissemination after 2 years.

**Magnetic Resonance Imaging Versus Lumbar CSF Cytology**

In 65 patients, both lumbar CSF cytology and spine...
Tumor staging using intracranial CSF cytology

MR imaging were performed perioperatively. Twelve of 65 MR imaging studies showed leptomeningeal enhancement, and 5 of 65 lumbar CSF samples were positive for tumor cells. Three of 65 results were concordantly positive, and 51 of 65 were concordantly negative. Eleven cases were discordant: in 9 cases lumbar CSF was negative and MR imaging was positive, and in 2 the reverse was true. The discordance percentage is 17%, with a kappa statistic of 0.27. Of the 2 patients with positive lumbar CSF cytology and negative MR imaging, one was treated clinically as having disseminated disease, and survived without recurrence until the present time (for 14 months). The other patient was not treated as having disseminated disease; that patient died of local recurrence. Of the 9 patients with positive MR imaging and negative lumbar CSF cytology, 7 were treated clinically as disseminated. Three of those survived without recurrence and 4 others died, 3 from disseminated disease and 1 from causes unrelated to the tumor. Two of the 9 were treated clinically as having nondisseminated disease, with one surviving and the other dying of primary tumor and chemotherapy complications.

Magnetic Resonance Imaging Versus Intracranial CSF Cytology

In 52 patients, both intracranial CSF cytology and spine MR imaging was performed perioperatively. Seven of 52 MR images showed leptomeningeal enhancement, and 9 of 52 intracranial CSF samples were positive for tumor cells. Four of 52 results were concordantly positive, and 40 of 52 were concordantly negative. Eight cases were discordant: in 3 cases intracranial CSF was negative and MR imaging was positive, and in 5 the reverse was true. The discordance percentage is 15%, with a kappa statistic of 0.41. Of the 5 patients with intracranial CSF positivity and negative MR imaging, 2 were treated clinically as having disseminated disease and 3 were not. These patients have survived without recurrences or evidence of subsequent dissemination for a minimum of 3 years, except for 1, who is alive and free of recurrence at 24 months. The latter patient had positive results for both lumbar and intracranial CSF evaluation, and was treated clinically as having disseminated disease. Of the 3 patients with positive MR imaging and negative CSF findings, the tumors in all 3 were treated clinically as disseminated. One patient subsequently died of disseminated disease, and the other 2 remain alive and disease free.

Kaplan-Meier Survival Analysis

Patients with a positive and negative result on perioperative neuraxis MR imaging had a median survival of 26.8 and 33.1 months, respectively (p = 0.02). Patients with a positive and negative result on perioperative lumbar CSF cytology evaluation had a median survival of 20.1 and 31.4 months, respectively (p = 0.11). Patients with a positive and negative result on intracranial CSF cytology evaluation had a median survival of 31 and 31.4 months, respectively (p = 0.85).

Discussion

Brain tumors are unique in that they primarily spread via CSF pathways. This may be more common in tumors that are close to the ventricular system, such as ependymomas and midline tumors; that is, PNETs. The MR imaging and CSF cytology techniques have replaced CT myelography as screens for detecting disseminated CNS malignancies. However, both techniques can yield false-positive and false-negative results. According to current protocols, evidence of tumor in either neuraxis MR images or lumbar CSF cytology leads to a diagnosis of disseminated disease. The site of CSF sampling has been a point of debate. Intracranial CSF can be readily obtained at the time of surgery or via ventriculostomy. However, there is some evidence that intracranial CSF sampling may yield a high false-positive rate, due to sloughing of tumor cells at the time of surgery. Thus, in most treatment protocols only lumbar CSF is considered diagnostic. The idea that different CSF sampling sites may yield different cytology results has been explored in several studies. Murray et al. examined 4 adult patients with CNS tumors and clinical evidence of dissemination. These authors showed that ventricular and lumbar CSF samples were significantly different with respect to the malignant cell count as well as protein and glucose concentrations. Rogers et al. studied 14 adult patients with clinical evidence of dissemination, and showed that there was a discordance percentage of 25% in the cytology of cisternal and lumbar CSF.

Gajjar et al. conducted an analogous although prospective study, focusing on the pediatric population. They selected 52 consecutive pediatric patients who had both a primary CNS neoplasm and a VP shunt. The authors performed simultaneous lumbar punctures and shunt taps during diagnosis or follow-up. Some patients had more than 1 sampling performed, yielding a total of 90 paired samples. The authors found that 11 samples were concordantly negative at both sites, 65 were concordantly positive at both sites, and 14 were discordant. Of those 14, in 12 the cytological findings from shunt CSF were negative, but those from lumbar CSF were positive, and in 2 patients the reverse was true. Based on this, the authors concluded that malignant cells were detected at a significantly higher rate in lumbar CSF than in shunt CSF.

There are several problems in both the setup and the interpretation of results of the aforementioned study. The VP shunt criteria for patient selection introduced a selection bias by excluding patients who did not require pre- or postoperative VP shunt placement. Also, the sample collection was performed at various points of the disease course, ranging from diagnosis to treatment follow-up. The results of the study merely demonstrate that different sampling sites yield discordant cytology results. However, given that there was no correlation of differences with outcome, it is not possible to infer that one site has a higher detection rate than the other. The false positives and false negatives were not accounted for in reaching that conclusion.

In our study we examined a larger population size and compared CSF cytology results with MR imaging results and with long-term outcome. Although MR imaging can detect most cases of dissemination, it is clear that CSF analysis can detect additional cases of dissemination at an earlier stage. We thus compared all 3 methods.
When comparing neuraxis MR imaging with intracranial CSF cytology, it appears that the latter reports dissemination more often than MR imaging. The discordance percentage is 15\%, with a kappa statistic of 0.41. From these results, it appears that there is a significant difference in detection and nondetection of disseminated disease by the 2 methods. When evaluating disease progression, intracranial CSF cytology identified 1 patient with disseminated disease that was not picked up by perioperative MR imaging. This patient was clinically treated as having disseminated disease, based on positive perioperative intracranial and lumbar cytologies. Although in this case, lumbar CSF cytology also identified this patient as having disseminated disease, as mentioned previously, there are instances in which intracranial CSF is the only study positive for perioperative dissemination. In the latter patient, MR imaging findings suggested disseminated disease only 3 months later. This finding demonstrates that cytology can detect dissemination before imaging. From long-term outcomes evaluation, it appears that both methods are prone to over- or underdiagnosing disseminated disease.

To compare the predictive value of individual perioperative diagnostic test results on survival, we constructed Kaplan-Meier curves comparing the survival of patients who had positive or negative results on neuraxis MR imaging and lumbar and intracranial CSF cytologies. We found that patients with a positive perioperative neuraxis MR imaging study had a 6.3-month lower median survival than those with negative perioperative neuraxis MR imaging results (p = 0.02, Fig. 1). Based on these data, a positive perioperative neuraxis MR imaging study is negatively correlated with survival. We found that patients with positive results on perioperative lumbar CSF cytology had an 11.3-month lower median survival than those with negative results on this evaluation; however, this difference was not statistically significant (p = 0.11, Fig. 2). A larger population size may be needed to demonstrate statistical significance. The survival analysis for patients with positive and negative results on perioperative intracranial CSF cytology yielded the finding that the 2 groups were not statistically different (p = 0.84, Fig. 3).

### Table 1: Correlation of intracranial and lumbar CSF cytology, and neuraxis MR imaging findings for reporting of disseminated disease

<table>
<thead>
<tr>
<th>Paired Samples</th>
<th>No. of Cases</th>
<th>Paired Samples</th>
<th>No. of Cases</th>
<th>Paired Samples</th>
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<td>LCSF+/MRI−</td>
<td>51</td>
<td>ICSF−/MRI−</td>
<td>40</td>
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<td>LCSF+/MRI+</td>
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<td>2</td>
<td>ICSF+/MRI−</td>
<td>5</td>
</tr>
<tr>
<td>LCSF−/ICSF−</td>
<td>5</td>
<td>LCSF−/MRI+</td>
<td>9</td>
<td>ICSF−/MRI+</td>
<td>3</td>
</tr>
<tr>
<td>total</td>
<td>40</td>
<td>65</td>
<td>52</td>
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</table>

*ICSF+ = intracranial CSF cytology positive for malignant cells; LCSF− = intracranial CSF cytology negative for malignant cells; LCSF+ = lumbar CSF cytology positive for malignant cells; ICSF− = lumbar CSF cytology negative for malignant cells; MRI+ = neuraxis MR imaging positive for leptomeningeal enhancement; MRI− = neuraxis MR imaging negative for leptomeningeal enhancement.
Tumor staging using intracranial CSF cytology

![Graph: Kaplan-Meier plots comparing survival of patients with (ICSF+) and without (ICSF-) malignant cells noted on perioperative cytological evaluation of lumbar CSF (p = 0.11).](image)

3. Based on these data, it seems that perioperative intracranial CSF cytology findings do not correlate with long-term survival.

Conclusions

Intracranial and lumbar CSF cytology findings were compared with each other and with neuraxis MR imaging in perioperative screening for disseminated pediatric medulloblastoma, supratentorial PNET, and ependymoma. We report detection rates based on each method. In addition, we compared discordance percentages and kappa statistics between the 3 methods examined. There is a discordance percentage of 15%, with a kappa statistic of 0.41, and of 17%, with a kappa statistic of 0.27, between neuraxis MR imaging and intracranial and lumbar CSF cytology, respectively. There is a discordance percentage of 18%, with a kappa statistic of 0.36, between intracranial and lumbar CSF cytology. We documented 1 case in our series in which dissemination was detected perioperatively by intracranial CSF cytology, but by neither lumbar CSF cytology nor neuraxis MR imaging. Isolated intracranial CSF positivity for malignant cells may represent an earlier stage of disease dissemination and may be associated with longer survival. Furthermore, none of the 3 screening methods is flawless, and their complementary use can reduce the incidence of missed or delayed diagnoses. Kaplan-Meier survival analysis showed that perioperative neuraxis MR imaging findings are correlated with survival, whereas perioperative lumbar or CSF cytology findings are not. Future studies with larger populations and long-term evaluation are needed to determine unequivocally the sensitivity and specificity of neuraxis MR imaging and lumbar and intracranial CSF cytology in screening for tumor dissemination.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Terterov, Krieger, McComb. Acquisition of data: Terterov, Bowen. Analysis and interpretation of data: Terterov, Krieger. Drafting the article: Terterov. Critically revising the article: Terterov, Krieger, McComb. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Terterov, Bowen. Study supervision: Terterov.

References


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