Atypia predicting prognosis for intracranial extraventricular neurocytomas

Clinical article

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Object. The literature, at present, provides limited information about extraventricular neurocytomas (EVNs) and is almost exclusively composed of case reports or small case series. Treatment for EVNs has largely been guided by results from central neurocytoma outcome studies. The authors present an analysis of all reported intracranial EVN cases to establish if tumor histopathological features can stratify EVN into groups with differing prognosis and help guide treatment decisions.

Methods. The authors identified studies reporting histology, treatment modality, and outcomes for patients with intracranial EVN. The rates of recurrence and survival for patients were compared using Kaplan-Meier analysis. Atypical tumors, defined by MIB-1 labeling index exceeding 3% or atypical histological features, were compared with typical tumors, and patients 50 years of age or older were compared with those younger than 50 years of age.

Results. Eighty-five patients met the inclusion criteria, and 27% of them had an atypical histology. Typical EVNs had a better prognosis than atypical EVNs after primary treatment, with a 5-year recurrence rate of 36% compared with 68% (p < 0.001), and a 5-year mortality rate of 4% compared with 44%, respectively (p < 0.001). Age younger 50 years was associated with a better prognosis than age equal to or greater than 50 years, with a 5-year recurrence rate of 33% and 74%, respectively (p < 0.001), and a 5-year mortality rate of 4% and 52%, respectively (p < 0.001). Multivariate analysis demonstrated that atypical EVNs carried significantly increased risk for recurrence (hazard ratio [HR] 4.91, p < 0.001) and death (HR 22.91, p < 0.01). Gross-total resection was superior to subtotal resection (STR) alone in tumor control rates for typical EVNs (95% and 68%, p < 0.05), and there was a trend for adjuvant external-beam radiotherapy to benefit STR. There was suggestion of similar trends in patients with atypical EVNs.

Conclusions. There are at least 2 distinct histological subtypes of EVN, with different prognostic significances. Atypia or MIB-1 labeling index greater than 3% is a significant predictor of poor prognosis for EVNs. Complete resection or more aggressive attempts at providing adjuvant therapy following STR appear to improve the prognosis for patients with EVNs. Although the authors’ results are informative, there are limitations to their analysis. Given the relatively modest total number of cases reported, as well as the nature of the disaggregated analysis, the authors were not able to use formal meta-analytical methods to limit the impact of between center heterogeneity. Additionally, they were not able to control for individual differences in data analysis and presentation across the different studies included in their analysis. (DOI: 10.3171/2011.9.JNS10783)

Key Words • extraventricular neurocytoma • MIB-1 • age • surgery • radiotherapy • recurrence • oncology

Abbreviations used in this paper: EVN = extraventricular neurocytoma; GTR = gross-total resection; HR = hazard ratio; STR = subtotal resection.
common, their diagnosis is frequently difficult to make and relies heavily on the judicious use of immunohistochemical analysis and electron microscopy. 3,52 Although EVNs may resemble central neurocytomas, it has been suggested that EVNs are associated with worse prognosis and a more aggressive biological nature. 41 In the present article, we present an analysis of all reported intracranial cases to establish if tumor histopathological features can allow further substratification of EVN into groups with differing prognoses.

Methods

Article Selection

Articles were identified using a PubMed search for “neurocytoma,” “neurocytomas,” “extraventricular,” and “central” alone and in combination. We subsequently searched the references in these articles for further reports. Inclusion criteria included documentation of individual, disaggregated patient data for the following: age, tumor location, histopathological description, treatment description, follow-up duration, and recurrence and mortality data.

Data Extraction

For each article, age, tumor location, treatment modality, histopathological report, follow-up duration, and recurrence and mortality data were extracted for individual patients. Tumor location is summarized in Table 1. Patients with intraventricular or extracranial tumors were excluded.

Histology Classification

Tumors were classified into either a typical or an atypical category. Atypical tumors were defined by MIB-1 labeling index greater than 3%, or features consistent with higher-grade tumors defined as frequent mitoses, vascular proliferation, or presence of necrosis.45

Statistical Analysis

Continuous variables are presented with standard error, and differences across these variables were analyzed using a 2-sided independent-samples t-test. We analyzed differences in categorical variables using the Pearson chi-square test. Kaplan-Meier estimates were used to generate survival curves. Differences in time to recurrence or death from disease were analyzed using the log-rank test. Cox proportional hazard modeling was used to determine HRs and to assess for differences in recurrence and survival, adjusting for differences in preoperative variables. Statistical tests were considered significant when p < 0.05. All descriptive and statistical analyses were performed using SPSS version 16.0 (IBM/SPSS).

Results

Results of the Systematic Review

Our search identified 35 articles reporting on 85 patients with intracranial EVNs meeting our inclusion criteria. The demographic data for all patients, additionally substratified by histology type, are summarized in Table 2.

Outcomes for EVNs have a Bimodal Distribution Depending on Histological Subtype

Of the 85 EVNs reported in the literature, 27% were atypical (23 of 85 patients). In 56 patients (66%) atypia was defined by MIB-1 labeling, while in 29 patients (34%) this determination was based on histology. Kaplan-Meier analysis demonstrated significant differences between patients with typical and those with atypical tumors in post–primary treatment 5-year recurrence rate (36% and 68%, respectively; p < 0.001, log-rank test) and 5-year mortality rate (4% and 44%, respectively; p < 0.001, log-rank test) (Fig. 1). The median time to recurrence after initial treatment was 48 months (range 6–216 months) for typical tumors and 21 months (range 5–94 months) for atypical tumors. Only 2 patients in whom histology was typical died during the follow-up course, 1 at 23 months and 1 at 312 months following primary treatment. The median time to death during the follow-up period after initial treatment for patients with atypical tumors was 42 months (range 6–98 months).

Impact of Age on Posttreatment Prognosis of EVNs

Given other reports of a possible association between age and outcomes for patients with EVNs, we assessed the impact of age on prognosis. Analyzing recurrence data by decade of life, we found a sharp increase in recurrence rates in patients in their 6th decade and above (Table 3). Thus, we performed a Kaplan-Meier analysis on overall recurrence risk for patients ≥ 50 years of age. Kaplan-Meier analysis demonstrated significant differences between patients younger than 50 years age and those 50 years of age or older in post–primary treat-
Atypia and prognosis in extraventricular neurocytomas

TABLE 2: Summary of demographic and lesion-related data in cases of typical or atypical EVN reported in the literature

<table>
<thead>
<tr>
<th>Variable</th>
<th>Typical</th>
<th>Atypical</th>
<th>All</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of lesions</td>
<td>62</td>
<td>23</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>52%</td>
<td>35%</td>
<td>48%</td>
<td>NS</td>
</tr>
<tr>
<td>age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (yrs)</td>
<td>27</td>
<td>50</td>
<td>32</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SE (yrs)</td>
<td>2.4</td>
<td>3.7</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>range (yrs)</td>
<td>2–76</td>
<td>5–76</td>
<td>2–76</td>
<td></td>
</tr>
<tr>
<td>≥50 yrs</td>
<td>10%</td>
<td>57%</td>
<td>22%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>cystic</td>
<td>31%</td>
<td>17%</td>
<td>27%</td>
<td>NS</td>
</tr>
<tr>
<td>calcified</td>
<td>13%</td>
<td>10%</td>
<td>12%</td>
<td>NS</td>
</tr>
<tr>
<td>median follow-up (mos)</td>
<td>24</td>
<td>27</td>
<td>24</td>
<td>NS</td>
</tr>
</tbody>
</table>

TABLE 3: Recurrence rates across all follow-up periods in 35 articles, stratified by decade

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Recurrence Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–9</td>
<td>18.8</td>
</tr>
<tr>
<td>10–19</td>
<td>10.0</td>
</tr>
<tr>
<td>20–29</td>
<td>20.0</td>
</tr>
<tr>
<td>30–39</td>
<td>18.2</td>
</tr>
<tr>
<td>40–49</td>
<td>23.1</td>
</tr>
<tr>
<td>50–59</td>
<td>50.0</td>
</tr>
<tr>
<td>&gt;60</td>
<td>64.3</td>
</tr>
</tbody>
</table>

ment 5-year recurrence rate (33% and 75%, respectively; p < 0.001, log-rank test) and 5-year mortality rate (4% vs 52%, respectively; p < 0.001, log-rank test).

Given that both histological features of atypia, as well as patient age ≥ 50, appeared, in a univariate analysis, to predict a worse prognosis for patients, we performed a Cox regression analysis for risk of recurrence and death posttreatment. After statistical regression, we found that only histological features of atypia remained a significant predictor of recurrence (HR 4.91, 95% CI 1.96–12.35, p < 0.001) and mortality (HR 22.91, 95% CI 2.82–185.98, p < 0.01). Thus, the significance of older age in univariate analysis is likely related to the high rate of atypical histology found in patients 50 years and older (68% vs 15%, respectively; p < 0.001, chi-square test).

Extent of Resection Predicting Recurrence in Typical EVNs

The extent of resection and adjuvant treatment data were available for 75 patients. Given that tumor histopathology independently affects tumor recurrence, we substratified the extent of resection by atypical or typical histology (Fig. 2). We found that in cases of typical EVNs, overall recurrence rates were 5% after GTR (1 of 20) and 32% after STR (6 of 19) (p < 0.05, chi-square test). Subtotal resection with adjuvant radiotherapy was associated with a 17% recurrence rate (1 of 6), which was not significantly different than STR alone (chi-square [not significant]). Also of note, in cases of GTR with adjuvant radiotherapy, there were no recurrences of the typical tumors.

Given the overall rarity of EVNs, and particularly atypical EVNs, the population size did not lend itself to statistical analysis for resection extent subgroups. To summarize the published literature on this topic, we found post–primary treatment recurrences for atypical EVNs included 2 of 2 patients receiving STR, 1 of 3 patients receiving GTR, and 4 of 11 patients receiving STR with adjuvant radiotherapy.

Discussion

Because data suggest a worse prognosis in patients with EVNs than in those with central neurocytomas, EVN has been listed as a distinct entity in the new WHO guidelines. However, these observations have been based on individual case reports and case series. Furthermore, due to the rarity of this tumor, worsened outcomes with atypical histology have been inferred from reports on central neurocytoma outcomes, and the existence of a higher tumor grade has not been formally demonstrated for EVNs. We found that atypical histology significantly predicts poor outcomes with higher recurrence and mortality rates. Additionally, we provide some evidence supporting the beneficial effects of a more aggressive surgery.

Analysis of patient outcomes revealed that atypical
histology predicted significantly higher rates of recurrence and mortality. Atypical pathology included either MIB-1 labeling index greater than 3%, or atypical histological features of frequent mitoses, vascular proliferation, and necrosis. We found that atypical tumors occurred in 27% of EVN cases and had 2 to 3 times the recurrence risk of typical EVNs, as well as recurring at a much earlier time posttreatment. Likewise, patients harboring tumors with atypical histology had a 10-fold increased risk of death during a follow-up period of 98 months.

Rades and colleagues have reported a 25% rate of atypical histology in central neurocytoma. Atypia and high MIB-1 labeling index have been demonstrated to be significant risk factors in central neurocytomas as well. Recurrence and mortality rates for typical central neurocytomas are not dissimilar from those we found for typical EVNs: 28% recurrence and 5% mortality in typical central neurocytoma compared with 36% recurrence and 4% mortality in typical EVNs. Atypical features appear to lead to higher rates of recurrence and mortality in both central neurocytomas and EVNs: 40% recurrence and 20% mortality in atypical central neurocytoma compared with 68% recurrence and 44% mortality, respectively, in atypical EVNs. The similar histology and clinical behavior of both central and extraventricular neurocytomas may argue against the idea that the EVN is actually a distinct disease from central neurocytoma. Although the higher rates of recurrence and mortality observed in atypical EVNs, compared with atypical central neurocytomas, could be explained by differing tumor biology, we believe that this likely reflects the relationship between the anatomical localization of tumor growth and symptom appearance. Atypical central neurocytomas may cause symptoms of hydrocephalus that lead to presentation at a much earlier stage by obstructing the narrow outflow tracts of the ventricular system. Cortical based EVNs may not cause symptoms until they are much larger in size and may be in closer proximity to critical neurovascular structures. These differences could potentially lead to earlier intervention and a higher chance of GTR without complications in atypical central neurocytoma. In fact, GTR was achieved in 33% of atypical central neurocytomas compared with 13% of atypical EVNs.

Prior reports have suggested that age may be a risk factor for poor prognosis in EVNs. Analysis of the published literature demonstrated age over 50 years is a risk factor in isolation. However, when rates of higher-grade tumors are controlled for using regression analysis, age does not appear to be an independent risk factor. Regardless, given the associations of atypia and age with poor outcomes, these data suggest that atypical histology and older age may be in the same epidemiological pathway in tumor progression for EVNs.

The extent of resection and adjuvant treatment is commonly correlated with patient outcomes in a variety of tumor types. In patients with central neurocytoma, GTR or STR with adjuvant radiotherapy results in superior rates of tumor control than STR. Our analysis demonstrates that GTR of EVNs results in significantly lower recurrence rates than STR alone in typical tumors, and there is a suggestion that adjuvant radiotherapy may improve recurrence rates following STR. Based on the
limited available data, both GTR and STR with adjuvant radiotherapy appear to offer better posttreatment tumor control rates for atypical EVNs. It is important to note that GTR is often difficult to achieve in cases of atypical EVNs, and in our review we found only 13% of atypical tumors received GTR.

Although our results are informative, there are limitations to our analysis. Given the relatively modest total number of cases reported, and the nature of our disaggregated analysis, we were not able to use formal meta-analytical methods to limit the impact of between-center heterogeneity. Of note, however, individual centers typically do not have enough cases to determine a quantitative measurement of heterogeneity that would be needed in a meta-analysis. The statistical methods in this paper use the individual patient data approach to combine disaggregated data to achieve survival estimates. This method has been validated compared with other fixed-effects models, and the Cochrane Collaboration considers it the optimal approach for survival analysis.9 Our results are, however, a summary of the literature and reliant on the quality of the composite studies and could therefore suffer from selection bias and source study bias. Furthermore, given the heterogeneity of treatment and relatively modest total patient number, we could not control for the extent of resection and adjuvant treatment effects in a multivariate analysis. Additionally, we were not able to control for individual differences in data analysis and presentation across the different studies included in our analysis. Thus, this study is not the ideal form of meta-analysis and does not, and cannot, conform to formal standards of meta-analysis. While review of Class III data is less than ideal, in the case of these tumors, it probably represents the best available attempt to consolidate information on an uncommon lesion because Class I data probably will never be available; yet clinicians still need to treat these patients. This effort represents the best effort to work within this context to provide some guidance on the prognosis and management of these rare lesions.

Conclusions

We provide data supporting the existence of at least 2 distinct histological subtypes of EVN, with different prognostic significances. Notably, these findings confirm that atypia is a significant predictor of poor prognosis specifically for EVNs. Furthermore, complete resections or more aggressive attempts at providing adjuvant therapy following STR appear to improve the prognosis for patients with typical and perhaps atypical EVNs. Given the high mortality rate of atypical EVNs even with adjuvant radiotherapy, future studies should focus on determining successful chemotherapy regimens and identifying novel molecular markers for targeted adjuvant therapies.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Parsa, Kane, Sughrue, Rutkowski, Lehil, Fang. Acquisition of data: Kane, Aranda, Mills, Lehil. Analysis and interpretation of data: Parsa, Kane, Sughrue, Aranda, Mills, Lehil, Fang. Drafting the article: Parsa, Kane, Sughrue, Rutkowski, Lehil, Fang. Critically revising the article: Parsa, Kane, Sughrue, Rutkowski, Aranda, Mills. Statistical analysis: Kane, Sughrue. Study supervision: Parsa.

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