Current Literature
In Clinical Science

Focal Cortical Dysplasia-Associated Tumors: Resecting Beyond the Lesion

Epilepsy Surgery of Focal Cortical Dysplasia–Associated Tumors

The goal of the present study was to evaluate the clinical characteristics and postoperative seizure outcome of epileptogenic tumors associated with focal cortical dysplasias (FCDs) compared to both solitary FCD type I and solitary tumors. Particular attention is given to FCD type IIIb (tumors associated with FCD type I), which have been recently classified as a separate entity. We retrospectively reviewed the clinical charts of 1,109 patients who were operated on for drug-resistant focal epilepsy, including 492 patients with a histologic diagnosis of solitary FCD I and II (83 and 157 cases, respectively), solitary tumors (179 cases), and FCD-associated tumors (73 cases, 58 of which met the criteria of FCD IIIb of the new International League Against Epilepsy (ILAE) classification). The different subgroups were evaluated for clinical characteristics and postoperative surgical outcome. Clinical variables and postoperative seizure outcome of patients with coexisting tumor and FCDs (FCD IIIb and tumor associated FCD II) were similar to those of patients with a solitary tumor and differed significantly from patients with solitary FCDs. Nevertheless, tumors associated with FCDs are characterized by a striking male predominance and a higher seizure frequency as compared to solitary tumors. Patients with drug-resistant focal epilepsy secondary to a solitary tumor or with a tumor-associated FCD have similar basic clinical presentation and postoperative seizure outcome. Nevertheless, the epileptogenic contribution of the associated FCDs can be crucial, and it needs to be adequately assessed. The impact of FCD on tumor-related epilepsy deserves future research in order to optimize the surgical strategies aimed at seizure relief.

Commentary
Low-grade supratentorial tumors constitute 10 to 40% of the pathological diagnoses in patients following resective surgery for refractory focal-onset epilepsy (1, 2). The most common tumor subtypes in this group include inherently indolent and intrinsically epileptogenic gangliogliomas (GG) (3) and dys-embryoplastic neuroepithelial tumors (DNT). Temporal lobe tumors in this group exhibit certain distinct features. About 90% of such tumors were found within or adjacent to the gray–white junction or hippocampal formation with frequent involvement of associated mesial temporal structures (4, 5). Several studies have identified young age, male predominance, long history of refractory epilepsy, healthy neurological examination, an indolent biological nature with long-term survival, and favorable surgical outcome as common characteristics in this group (6, 4, 5). Supratentorial GG and DNT tumors demonstrate a strong association with focal cortical dysplasias (FCD). It is notable that FCD are a common cause of intractable epilepsy in both children and adults. It is well-known that FCD are associated with epileptogenic brain tissue, although surgical resection achieves seizure control to a variable extent (7, 8). The optimal surgical strategy for these patients continues to be debated. Some centers typically recommend, when possible, isolated tumor resection while others include resection of surrounding epileptogenic structures guided by electrocorticography (ECoG). Such ECoG studies have challenged the idea that epilepsy in a subgroup of FCD is associated with a solitary epileptogenic lesion. That is, epileptogenic areas remote from the primary dysplastic lesion are often associated with less favorable clinical outcomes. All forms of FCD lead to disorganization of the normal structure of the cerebral cortex. Characteristic findings include often subtle aberrant radial or tangential lamination of the neocortex (FCD Type I) and/or cytological abnormalities (FCD Type II). FCD in combination with GG and DNT tumors appear to occur isolated in temporal and/or extratemporal regions. In particular, FCD Type I is associated with subtle neuroimaging, histopathology, and less favorable post resective seizure outcomes. The indolent progression and associated epileptogenicity of glioneural tumors have raised the hypothesis of a developmental rather than neoplastic origin of these lesions (9).

A recent International League Against Epilepsy (ILAE) task force has re-evaluated available data and proposed a neuropathological classification system of FCD (10). The major modification to the previous classification includes the intro-
duction of FCD Type III, which occurs always in combination with mesial temporal sclerosis (FCD Type IIA), or with epilepsy-associated tumors (FCD Type IIIB). FCD Type IIIC is found adjacent to gliosis and vascular malformations, and FCD Type IIID is associated with all other lesions, such as encephalitis, in an epileptic brain. In contrast, FCD Type I refers to isolated lesions, which present either as radial (FCD Type IA) or tangential (FCD Type IB) cortical dyslamination, microscopically identified in one or multiple lobes. This three-tiered classification system can facilitate exploring clinico-electrocerebral features with associated epileptogenicity, neuroimaging relationships, and underlying molecular pathological mechanisms of FCD (7).

Cossu et al. published a single center retrospective study in which an extensive chart review was performed for 1109 patients who had a temporal or extratemporal resection for medically refractory epilepsy. The authors evaluated the clinical characteristics and postoperative seizure outcomes of patients following resection of epileptogenic glioneural tumors associated with FCD compared with both solitary FCD Type I and solitary tumors. The authors found that FCD IIIB significantly differed from solitary FCDs Type I in age at seizure onset, seizure frequency, presence of MRI findings, necessity for stereo-electroencephalography (SEEG) evaluation, site of surgery (temporal vs. extratemporal regions), and seizure outcome. FCD IIIB differed from solitary tumors in terms of gender, seizure frequency, and site of surgery (temporal vs. extratemporal regions).

The key finding of this study is that FCD IIIB demonstrates characteristics more similar to solitary tumors than to FCD I, including less challenging resection and improved seizure outcomes. The authors also report a slightly higher seizure frequency refractory to medication management detected in FCD IIIB patients. These findings may be due to a presence of cortical disorganization representing enhanced excitability within the epileptogenic zone. Usage of ECoG has challenged the idea that epilepsy in FCD is associated with a solitary epileptogenic lesion. ECoG data have demonstrated both epileptogenic discrete dysplastic foci and remote, structurally normal-appearing epileptogenic cortex (11, 12). The authors emphasize that solitary FCD Type I likely represents a more widespread structural abnormality compared with dysplastic FCD IIIB that share characteristics similar to discrete solitary tumors. The authors reported MRI-negative studies in 30% of their series. It is likely that FCD Type I contributes to extensive epileptogenic networks that include pathways connecting deep modulatory territories, such as thalamus and distant pathological neocortex. The FCD Type I associated ‘epileptic focus’ becomes a misnomer when such epileptic circuits are discussed. This hypothesis fuels the debate at two levels. First, does resective surgery provide favorable outcomes in patients with significant neuroimaging-positive FCD lesions? An important complementary discussion surrounds the localization methodology for GG and DNT tumors in the presence of FCD Type I. Specifically, it remains controversial whether ECoG provides useful information for potentially extending the resection beyond the boundaries of the tumor.

The authors emphasize that FCD Type IIIB appears to be correlated with the tumor rather than the FCD. The authors also set forth a statement that their analyses make the ILAE classification of FCD IIIB using strict histopathological criteria less relevant. Regardless of the study limitations that include a relatively small sample size, lack of a multicenter design, and retrospective approach, this study serves as an important platform on which to design and implement a larger collaborative effort attempting to understand the impact of FCD on tumor-related refractory epilepsy. In addition, the study provides an impetus for developing better detection methods and clarity of the contribution of these distributed epileptogenic foci potentially impacting surgical efficacy in patients with GG and DNT tumors.

by Marvin A Rossi, MD, PhD

References

American Epilepsy Society

Epilepsy Currents Journal

Disclosure of Potential Conflicts of Interest

Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.
This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.
This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (DGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships
Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.
Section #1 Identifying Information

1. Today’s Date: 5/14/2014

2. First Name  Marvin Last Name Rossi  Degree MD, PhD

3. Are you the Main Assigned Author? ☒ Yes ☐ No
   
   If no, enter your name as co-author:

4. Manuscript/Article Title: Focal Cortical Dysplasia-Associated Tumors: Resecting Beyond the Lesion to Disconnect Refractory Epileptic Circuits

5. Journal Issue you are submitting for: 14.5

Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

<table>
<thead>
<tr>
<th>Type</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Grant</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Consulting fee or honorarium</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Support for travel to meetings for the study or other purposes</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Fees for participating in review activities such as data monitoring boards, statistical analysis, end point committees, and the like</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Payment for writing or reviewing the manuscript</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Provision of writing assistance, medicines, equipment, or administrative support.</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Other</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This means money that your institution received for your efforts on this study.

** Use this section to provide any needed explanation.
**Section #3 Relevant financial activities outside the submitted work.**

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

<table>
<thead>
<tr>
<th>Type of relationship (in alphabetical order)</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Board membership</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Consultancy</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Employment</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Expert testimony</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Grants/grants pending</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Payment for lectures including service on speakers bureaus</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Payment for manuscript preparation.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Patents (planned, pending or issued)</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Royalties</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Payment for development of educational presentations</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Stock/stock options</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Travel/accommodations/meeting expenses unrelated to activities listed.**</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Other (err on the side of full disclosure)</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This means money that your institution received for your efforts.

** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

**Section #4 Other relationships**

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☑ No other relationships/conditions/circumstances that present a potential conflict of interest.

☐ Yes, the following relationships/conditions/circumstances are present:


Thank you for your assistance.  
_Epilepsy Currents_ Editorial Board