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Developmental tumors and adjacent cortical dysplasia: Single or dual pathology?

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Summary

Developmental tumors often lead to refractory partial seizures and constitute a well-defined, surgically remediable epilepsy syndrome. Dysplastic features are often associated with these tumors, and their significance carries both practical and conceptual relevance. If associated focal cortical dysplasia (FCD) relates to the extent of the epileptogenic tissue, then presurgical evaluation and surgical strategies should target both the tumor and the surrounding dyslaminated cortex. Furthermore, the association has been included in the recently revised classification of FCD and the epileptogenicity of this associated dysplastic tissue is crucial to validate such revision. In addition to the possibility of representing dual pathology, the association of developmental tumors and adjacent dysplasia may instead represent a single developmental lesion with distinct parts distributed along a histopathologic continuum. Moreover, the possibility that this adjacent dyslamination is of minor epileptogenic relevance should also be entertained. Surgical data show that complete resection of the solid tumors and immediately adjacent tissue harboring satellites may disrupt epileptogenic networks and lead to high rates of seizure freedom, challenging the epileptogenic relevance of more extensive adjacent dyslaminated cortex. Whether the latter is a primary or secondary abnormality and whether dyslaminated cortex in the context of a second lesion may produce seizures after complete resection of the main lesion is still to be proven.

KEY WORDS: Long-term epilepsy-associated tumors, Cortical dysplasia, Glioneuronal, Dual pathology, Developmental tumors.

Developmental Tumors and Cortical Dysplasia in the Surrounding Cortex: The Possible Relation

Developmental tumors are benign glioneuronal neoplastic lesions that rarely progress or lead to neurologic dysfunction, yet they often present with seizures (Becker et al., 2006). These tumors are usually localized in limbic and perilimbic cortex, are promptly identified with magnetic resonance imaging (MRI), and when associated with refractory seizures constitute a well-defined surgically remediable epilepsy syndrome (Friede et al., 1994; Thom et al., 2012). There are several possible mechanisms for the epileptogenicity associated with developmental tumors. In a simplified perspective, one is that the neuronal component of the tumor is in itself hyperexcitable and the other is that the tumor leads to epileptiform changes in the adjacent tissue (Blumcke, 2009). The fact that ictal or very intense interictal discharges are recorded directly from the tumors and also that a high percentage of patients are rendered seizure-free exclusively with complete lesion excision (Aronica et al., 2001; Giulioni et al., 2006) is in keeping with the first possibility, whereas the finding that ictal-onset zones may extend beyond the tumor would support the adjacent epileptogenicity hypothesis (Chassoux et al., 2012). There are two problems with this framework. One is that because incomplete resections of the ictal-onset/epileptogenic zones are usually accompanied by incomplete resections of the developmental tumors, the exact role of adjacent microscopical architectural disorganization on the remaining epileptogenicity

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cannot be directly inferred (Barba et al., 2011; Chassoux et al., 2012; Rydenhag et al., 2012). The other is that these two hypotheses disregard a third, namely, the possibility that epileptogenicity may indeed relate to adjacent dyslaminated cortex not directly induced by the tumor.

MRI and histopathology of both the tumors and the surrounding cortex have linked these lesions to focal cortical dysplasia (FCD), particularly FCD type 1, indexed by a dyslaminated, disorganized cortex (Becker et al., 2006; Blumcke, 2009; Blumcke & Spreafico, 2012; Thom et al., 2012). Because FCD is a major etiology of refractory epilepsies, the understanding that developmental tumors are often accompanied by adjacent FCD would suggest the association of two epileptogenic lesions, that is, *dual pathology*.

There are, however, at least two alternative perspectives: One is that both the tumor and the adjacent dysplasia are the *same lesion*, with distinct components along a developmental continuum. In other words, the complex "tumor/adjacent dysplastic cortex" could constitute a histopathologic spectrum, with tumor features at one and dysplastic features at the other end. In a series of patients with developmental tumors and associated pathologies, Prayson et al. (2010) found that the latter were usually FCD. However, as they point out, the nature of the relationship is unknown. Both could coexist on the basis of being caused by abnormal development, or else they could, as suggested earlier, be parts of the same lesions (). In this scenario, the associated dyslaminated portion may or may not be epileptogenic, and seizure freedom could be achieved in some patients with resection of the tumor mass only, whereas others would need a larger resection encompassing these architectural abnormalities in the vicinity of the mass. The third possibility is that the dysplastic features adjacent to the tumor are neither part of the "main" lesion nor a lesion on its own, and simply represent an incidental finding with minimal, if any, epileptogenic tendency, the resection of which would thus be irrelevant.

These distinct perspectives on the association between developmental tumors and adjacent dyslaminated or dysplastic cortex are depicted in Fig. 1 and have both practical and conceptual implications. If the tumor and the surrounding dyslaminated tissue are considered epileptogenic lesions on their own, surgical strategies should mirror other instances of dual pathology and aim at resection of both, preceded by determination of the spatial extent of the adjacent, putatively dyslaminated, epileptogenic cortex (Li et al., 1999; Kim et al., 2010). However, if both are part of the same histopathologic continuum or if the surrounding dyslaminated cortex is an incidental finding, the relevance of the latter for seizure generation would be questionable. In practice, this would suggest that patients could be seizure-free with lesionectomy and additional resection of variable

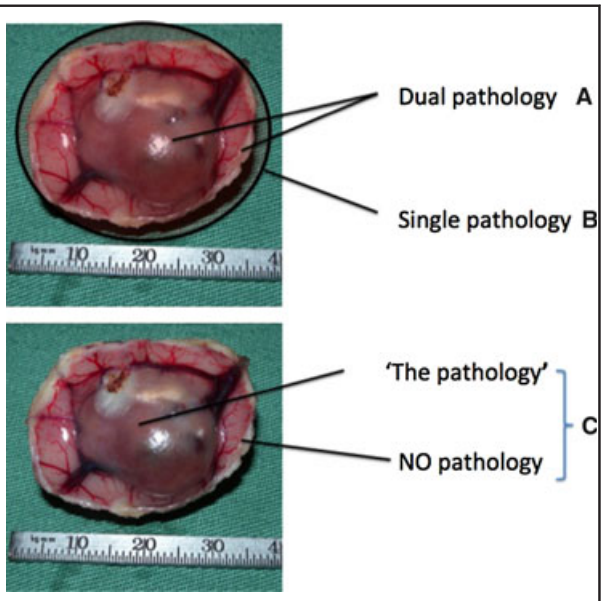

Figure 1.
Possible scenarios for the association of a developmental tumor and FCD. In (**A**) the tumor is one lesion and the putatively dyslaminated surrounding cortex is another (*dual pathology*); In (**B**) both the solid tumor and the surrounding cortex are one single lesion within a histopathologic continuum, whereas in (**C**) only the solid tumor is the lesion, and the adjacent cortex is irrelevant.

extent of adjacent tissue—*but without the need for a complete determination or resection of putative ictal onset zones, often more extensively distributed*. For instance, other types of developmental lesions, such as polymicrogyria, often harbor epileptogenic and nonepileptogenic areas, and seizure control can be achieved with partial resection of only the epileptogenic parts of the lesion (Chassoux et al., 2008).

An International League Against Epilepsy (ILAE) task force recently revised the classification of FCD and the major, explicit reason behind that effort was the perceived need to incorporate those situations in which dysplastic (i.e., dyslaminated) cortex was associated with another well-characterized lesion such as hippocampal sclerosis or glioneuronal tumors (Blumcke et al., 2011). In a way, this newly created category (type 3 FCD) would be rendered of limited relevance should dysplastic abnormalities surrounding these lesions prove to be incidental findings without epileptogenic tendency. Therefore, the debate on whether dyslamination adjacent to developmental tumors represents dual pathology must also be framed conceptually. Herein we review the evidence that informs this debate.

Imaging and Neurophysiologic Issues

The following is a practical case to begin this discussion. Barba et al. (2011) reported a patient with a lateral temporal ganglioglioma, who also had increased cortical thickness in the ipsilateral temporal pole suggestive of FCD. The initial resection prioritized the dysplastic abnormalities and missed the tumor; this did not control the seizures. A second surgery, preceded by extensive exploration with subdural electrodes, resected the tumor and the immediately surrounding tissue. Epileptic abnormalities were shown to colocalize with the small tumor mass. Of interest, there were no dysplastic changes adjacent to the tumor, although—as expected—collections of tumor cells ("satellites") were found in the vicinity. Unfortunately, because the tumor was missed in the first operation, neither the efficacy of an extended lesionectomy (i.e., lesionectomy with resection of adjacent cortex on the basis that some tumor satellites are usually found) nor the epileptogenic relevance of the dysplastic lesion in the ipsilateral temporal pole could be ascertained. This case also shows that FCD associated with developmental tumors may be at some distance and thus constitute a "true" second pathology—however, of debatable epileptogenic relevance. Whether mild dyslamination adjacent to tumors seen in other patients also may represent a second pathology is unclear.

Dysembryoplastic neuroepithelial tumors (DNTs) are the other developmental lesions frequently fueling this debate. A number of recent developments, led by the group that originally described this entity years ago, may streamline the understanding of the epileptogenic aspects of these lesions (Chassoux et al., 2012, 2013). Data comes from three sources: imaging, histopathology, and intracerebral electroencephalography (EEG). Classical histopathologic descriptions have shown that DNTs may be simple, complex, or nonspecific. It is easier to describe complex DNTs first: These are lesions characterized by a specific glioneuronal element (SGNE) associated with glial nodules and occasionally FCD. The simple form displays only the SGNE, *without glial nodules and the occasional FCD features,* and in the nonspecific form the glial and dysplastic components are similar to the complex forms but the SGNE is absent (Daumas-Duport et al., 1999; Chassoux et al., 2013).

Imaging-histopathologic correlations in DNTs suggest that magnetic resonance imaging (MRI) features are consistent with one of three main patterns with reasonably predictive histologic correlates (Chassoux et al., 2012, 2013). Some lesions are homogenous, well-delineated, cystic, or polycystic (type 1) and associated with the SGNE, whether in a simple or complex histology. MRI type 2 DNTs are nodular-like, heterogenous, mixed cystic and irregular solid components and with a nonspecific histology. The same nonspecific pathologic findings are associated with MRI type 3 DNTs, which are poorly delineated with gray-white matter blurring and thus more diffusely imbricated with the cortical tissue.

Our reading of this literature views patients as pertaining to one of two "anatomofunctional clusters": *cluster A* includes patients with type 1 or 2 MRI features; simple, complex, or nonspecific histopathology; and a preferred neocortical location, temporal or extratemporal. In contrast, *cluster B* refers to those with a nonspecific histopathology and type 3, more diffuse, MRI, usually located in the mesial or basal temporal lobe regions. We believe this is an important distinction because the associated dysplastic abnormalities traverse in the opposite direction in the histopathologic spectrum of DNTs—and this may be practically relevant: nonspecific DNTs have more dysplastic abnormalities than complex, which in turn outweighs simple DNTs.

As a next step, stereo-EEG (SEEG) evaluation of different types of DNTs allowed the incorporation of electrophysiologic (epileptogenic) data with the anatomic and histopathologic findings. The first point these studies make is that irrespective of the type of DNT, SEEG shows that ictal onset always involves the tumor (Chassoux et al., 2012). In "cluster A"—the mostly neocortical DNTs—onset usually colocalized with the lesion, whereas two thirds of the patients in "cluster B" had ictal-onset zones apparently more extensive than the tumor—however, mostly related to involvement of mesial temporal structures. Therefore, these mesial temporal DNTs pose the intriguing possibility that three lesions could coexist: the DNT itself, the associated dysplastic abnormalities, and mesial temporal sclerosis. Could it represent "triple pathology"? If so, to what extent does the associated dyslamination add to the epileptogenicity in the context of the other two lesions? In this large series, FCD was seen in 12 of 16 patients in whom the ictal-onset zone was more extensive than the lesion, and in half of the cases where the ictal zone colocalized with the tumor—irrespective of the MRI type. Because the epileptogenic zone tended to extend beyond the tumor mostly in cluster B—that is, MRI type 3, the more imbricated type—it is unclear whether associated dysplasia in the mesial temporal structures is more epileptogenic than that in the neocortex. Such uncertainties are compounded by the fact that it is also unclear if patients with less favorable outcomes did poorly because of incomplete resection of the epileptogenic zone extending beyond the lesion or because of incomplete tumor resection. Clarifying this would be *key to determining the role of "adjacent dysplasia,*" but unfortunately it is difficult to disentangle these two situations, because the majority of patients in whom the

epileptogenic zone was not completely resected also had incomplete resection of the tumor.

At the Porto Alegre Epilepsy Surgery Program we have been proposing a noninvasive presurgical evaluation protocol for patients with developmental tumors, which are then operated under acute electrocorticography (ECoG). In most patients with gangliogliomas and DNTs we find two distinct ECoG patterns: (1) very frequent, almost continuous spiking; and (2) occasional, intermittent spikes. The former is usually found over the tumor and its immediate surroundings, and every attempt is made to resect all regions that display these exquisitely epileptogenic discharges. On the other hand, intermittent, low-frequency spikes often persist at some distance on the postresection ECoG, and this has not affected the results (Figs. 2 and 3A,B). Those patients who present occasional recurrent seizures are those in whom we later find that portions of the tumor were left behind.

Surgical Contributions to the Debate

When the lesion is completely resected—with the appropriate margins to include neighboring satellites in gangliogliomas or immediately adjacent dysplastic abnormalities imbricated with the borders of DNTs—the remaining low-frequency ECoG discharges have proved irrelevant. The first 26 such patients with gangliogliomas were entirely seizure-free following >5 years of follow-up. Similar results have been reported from The Netherlands, where 23 (96%) of 24 patients with refractory seizures associated with gangliogliomas were rendered seizure-free by total resection of the tumor, an outcome reached in only 3 (17%) of the 17 with incomplete resections (Aronica et al., 2001). Clearly, acute ECoG (as well as more costly prolonged invasive EEG evaluation) shows that the bulk of epileptogenic abnormalities are within the

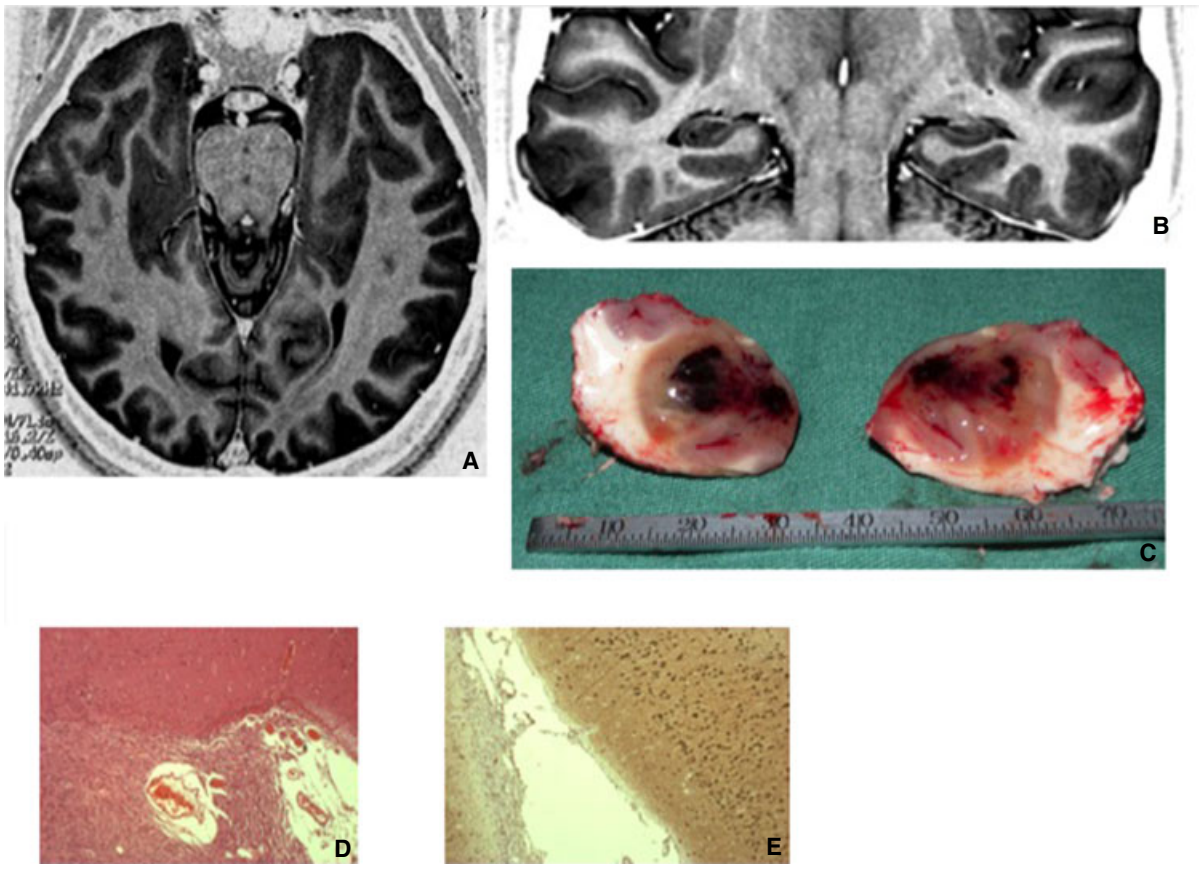

Figure 2.
Composite picture inversion recovery MRI sections depicting the lesion (**A**, **B**), macroscopic appearance (**C**), and histopathology (**D**, **E**) of an infantile desmoplastic astrocytoma (WHO I) in a 24 year-old woman with refractory partial seizures. Note the lesion and adjacent cortex in (**D** – HE × 50) and, more clearly, dyslaminated cortex adjacent to the lesion in (**E** – NeuN × 50).

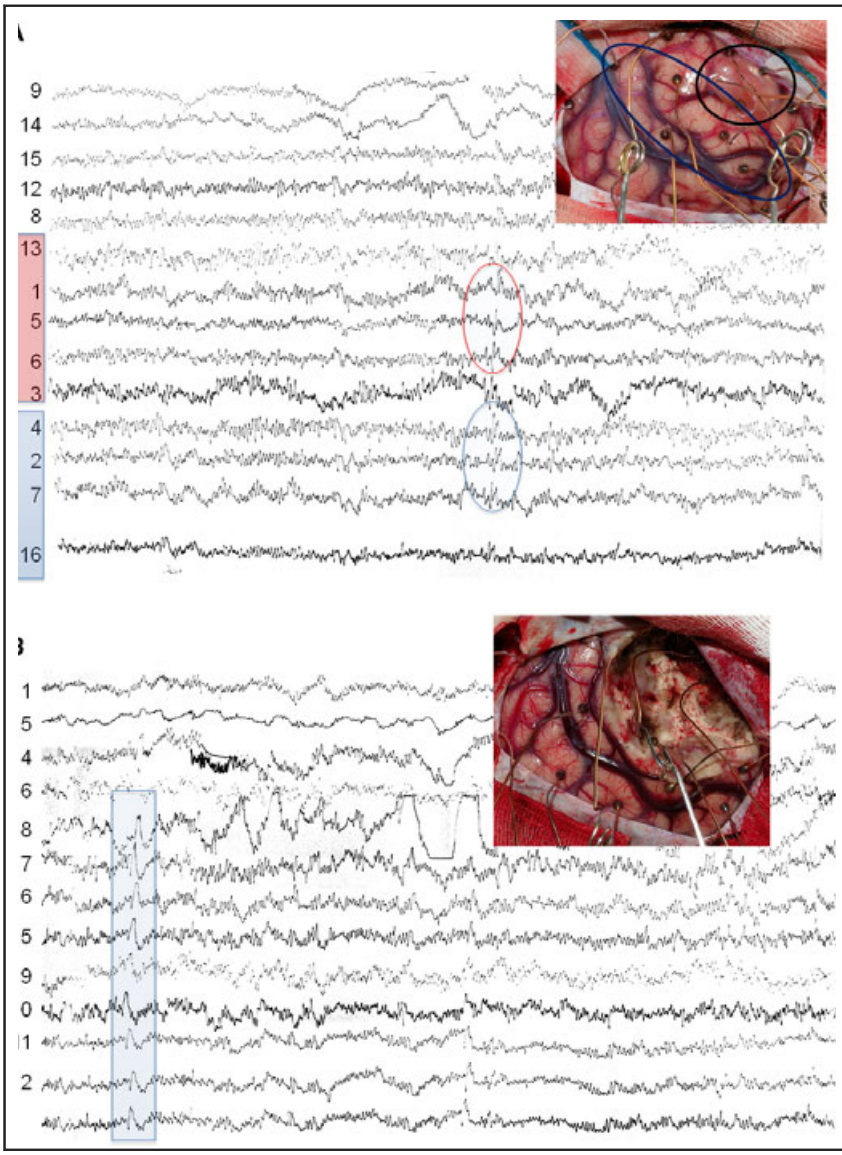

Figure 3.
Intraoperative preresection and postresection cortical views and ECoG samples of the same patient as Fig. 2. In (**A**), note spikes involving both the solid lesion (black line in the cortex and in the recording) and the immediately surrounding cortex (blue line in the cortex and in the recording). In (**B**), note persistence of spikes at some distance from the resection. The patient is now seizure-free for a year.
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ganglioglioma or in its immediate vicinity (Fig. 4). These findings raise the issue of whether it would be advantageous to guide resection by acute ECoG. In other words, if the literature is clear that complete resection of the ganglioglioma is both necessary and sufficient to render patients seizure-free, then the role of acute ECoG (as that of any other invasive evaluations) is in check. We have learned to guide resection of the immediate surrounding tissue according to frequent ECoG spiking (although, in most instances, these colocalize with the tumor). In addition, as mentioned earlier, it is our experience that the remaining intermittent spikes, at variable distances from the tumor, are not related to seizure relapse. This was further suggested by the recently reported findings from 49 patients with seizures associated with gangliogliomas operated in San Francisco (Southwell et al., 2012). Ninety-four percent of those who had a gross total resection were seizure-free, an outcome seen in only half of those with partial resection of the tumor. Of note, the majority of the patients in whom acute ECoG was used had persistent extralesional spiking in the final recording, and that had no relation to seizure outcome. Finally, the more meager results with lesionectomy alone (66% seizure freedom) reported by Giulioni et al. (2006) were associated with mesial temporal gangliogliomas, raising the issue of the involvement of mesial temporal lobe structures in the epileptogenicity of such patients. This, again, rekindles the lingering question of whether the mesial temporal structures—particularly the hippocampus—should be included in the resection when developmental tumors are in their vicinity. Although this is not the main focus of this article, it is hard to escape this debate, because the reason that surgery in some patients with DNTs and gangliogliomas fails to control seizures may relate to the (secondary) involvement of mesial temporal structures (i.e., mesial temporal sclerosis), and not to

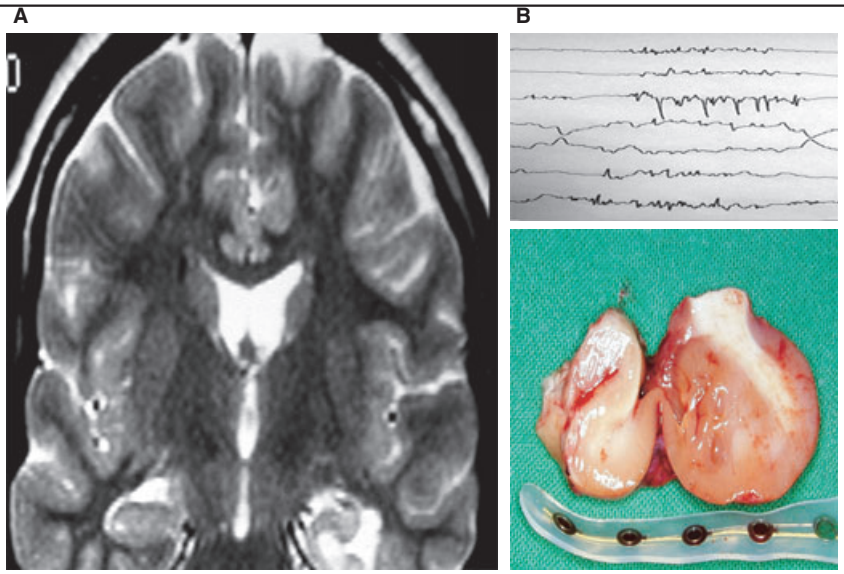

Figure 4.
Acute ECoG recording in a patient with mesial temporal ganglioglioma. (**A**) T_2-weighted coronal MRI depicting the tumor in the left mesial temporal lobe, associated with an atrophic ipsilateral hippocampus. (**B**) Excerpt from the acute ECoG recording with an eight-contact subdural strip. Plotting the recording electrodes against the resected tissue suggests maximal epileptiform activity exactly at the tumor.

surrounding cortical dyslamination that is left untouched. Furthermore, the issue of the relevance of microscopic dysplastic abnormalities associated with hippocampal sclerosis (HS) may apply to the present debate on the relevance of the same abnormalities in the context of developmental tumors. Therefore, the discussion on how conceptually and practically relevant the construct of "type 3A FCD" (dyslamination + hippocampal sclerosis) is, may be the same in regard to "type 3B FCD" (dyslamination + developmental tumor).

When the tumor involves the hippocampus, there is no doubt it should be included in the resection, as few functional deficits may be anticipated. However, the picture is less clear when the tumor is extrahippocampal—but in the anterior/inferior temporal lobe. Although as is usually the case in the observational field of epilepsy surgery, that the relevant studies have not been performed, the bulk of evidence favors the inclusion of the mesial structures in the resection of neocortical temporal lobe developmental tumors *only when there is unequivocal evidence of hippocampal sclerosis by MRI.* Other than this, very good results have been achieved with resection of the tumor while sparing healthy looking (and functionally preserved) hippocampi (Schramm et al., 2001; Morioka et al., 2007; Mintzer & Sperling, 2008; Elsharkawy et al., 2011). This issue intersects with that of the relevance of microscopic dysplastic changes in the temporal neocortex in patients with hippocampal sclerosis. Review of the pertinent literature suggests that conclusions on the epileptogenic relevance of the dyslaminated cortex may have been precipitate. The evidence supporting the notion of what appears to be an independent epileptogenicity in this microarchitecturally abnormal cortex is based on neurophysiologic evidence and derives from studies in which the hippocampus was always resected, in addition to what later proved to be FCD type 1 in the temporal neocortex (Fauser & Schulze-Bonhage, 2006; Kim et al., 2010). However, important evidence to the contrary comes from the surgical literature comparing long-term outcome of hundreds of *consecutive patients* with temporal lobe epilepsy due to HS operated through selective amygdalohippocampectomy or anterior temporal lobectomy. If microscopic dysplastic abnormalities are as common as suggested (Fauser & Schulze-Bonhage, 2006), many such patients should have had temporal dyslamination, and if the latter were epileptogenically relevant then results with larger resections should have been superior to those with the neocortex-sparing, more selective technique. This clearly was not the case, and the two techniques do not differ in seizure control, up to two decades after operation (Paglioli et al., 2006; Hemb et al., 2013).

Final Remarks

As tempting as it is to consider cortical dysplasia adjacent to developmental tumors as an independent pathology of epileptogenic relevance, the jury is still out. Perhaps instead of fueling the debate on the basis of histopatho-

logic, electrophysiologic, and imaging findings, a better effort will be to focus on the ultimate epileptologic relevance of dyslaminated cortex associated with many cortical disorders leading to seizures (Schwartzkroin & Wenzel, 2012). Whether these are primary or secondary abnormalities and whether dyslaminated cortex in the context of a second lesion may produce seizures after complete resection of the main lesion is achieved is still to be proven.

Disclosures

The authors have nothing to disclose. The authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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