Surgical treatment of low-grade epilepsy-associated with neuroepithelial tumors

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Brain tumors are a significant cause of hard-to-manage epilepsy, accounting for 20% to 30% of all refractory epilepsy surgery cases. In this group of patients, low-grade epilepsy-associated to neuroepithelial tumors (LEAT) are the main cause. The most frequent being dysembryoplastic neuroepithelial tumors (DNT) and ganglioglioma (GG). In this article, we review definition changes of refractory epilepsy, advances in diagnostic imaging, and histopathological diagnosis with new molecular markers, which have allowed for an increasingly early and accurate diagnosis. Resective surgery is also reviewed, allowing in these cases a seizure freedom close to 70-90% of patients. The best outcome in terms of seizure control can be achieved when early surgery is performed.

Keywords: *Epilepsy, tumor, surgery*

INTRODUCTION

Brain tumours represent an important cause of refractory epilepsy and account for 20-30 % of epilepsy surgery cases[1]. Among the most epileptogenic tumours are low-grade neuroepithelial tumours characterised by slow growth and low risk of malignancy. This group of tumours mainly includes disembryoplastic neuroepithelial tumours (DNTs) and ganglioglioma (GG), followed with less epileptogenicity by low-grade gliomas, meningioma, glioblastoma, metastases and lymphoma[2]. According to data from the European epilepsy registry bank published by Blümcke et al.[3] out of a total of 1551 tumours, 65 % were DNT and GG. Epilepsy-associated low-grade neuroepithelial tumours[3] encompass a broad spectrum of glial or glioneuronal tumours that mainly affect paediatric and young adult patients, and are associated with refractory epilepsy in 90-100% of patients[4][5]. This group of tumours was named in 2003 by Luyken et al.[6] as long-standing epilepsy-associated tumours (LEAT). This term has been abandoned in recent years, as the definition of refractory epilepsy does not currently consider a time frame[7], and the term low-grade epilepsy-associated neuroepithelial tumours has been adopted in recent years[3][8].

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Physiopathology

Intra-axial tumors compromising the cerebral cortex are related with higher frequency to epilepsy. Within this group, low-grade tumors are the most characteristic[8]. Generally, all the tumors can change surrounding brain tissue, due to various factors, such as, edema, mechanical effect, irritation, disturbance a level of the neural networks, local hypoxia and disturbance of the blood-brain barrier[9]. The highest epileptogenicity of low-grade tumors, could be explained by its slow growth, which would give way to epileptogenic mechanisms, given by intrinsic properties of the glioneural tumors. Among these properties we may find: disarrangement of neuronal and glial components, similar to cortical dysplasias, over expression of neurotransmitters, receptors and neuropeptides. All the foregoing could contribute to the creation of hyperexcitability sources[10]. Location is another one related with the epileptogenicity, so localized tumors regarding the frontal/temporal/ parietal/ cortex and especially those localized at eloquent areas have a higher frequency of correlation with epileptic seizures[11]. It is also believed that disturbances of neurotransmitters equilibrium, specifically glutamate and GABA, in tumors periphery contribute to epileptogenesis[11][12]. In this context, the correlation between IDH-1 mutation and increase of agonists of glutamate receptors has been described. On the other hand, there is a low GABA-mediated inhibitory activity in the peritumoral tissue.

Clinical Presentation

Low-grade neuroepithelial tumors, associated to epilepsy (LEAT), are characterized by onset of focal epileptic seizures with/without secondary spread from early life stages. The most frequent crisis pattern are focal crises with consciousness disorder. It is the only symptom in 30% to 50% of all cases. In 30% of cases, the crisis pattern may be mixed, with secondary spread described in 10% to 15%; focal crises, in 5%[13]. Neurological deficit is rare. average age of epileptic seizures onset is 16.5 years old. This group of patients had a long prior treatment period with anti-epileptic drugs (AEDs). The average period between the crisis onset and surgical treatment is 11.8 years[3]. 70% of these tumors are located in the temporal lobe. Most of them are Grade I benign tumors, according to the WHO[6], therefore, recurring tumors and progression have a low frequency.

Imaging studies

Preferred imaging study aimed to evaluate this type of tumors is Magnetic Resonance (MR). There is not a typical/pathognomonic pattern which allows us to properly lead the subtype of tumor, as imaging results are variable. Sometimes, it is difficult to differentiate a LEAT from a low-grade glioma, especially when the record of epileptic seizures is short or epilepsy onset is late. Most of these lesions are small, with no mass effect, and with no infiltrative component. Some have cystic features and may not have contrast uptake (Figure #1). Gangliomas are characterized in MR due to its link with cystic/nodular lesions. These may have contrast uptake. Besides, there may be a loss of differentiation between white matter and grey matter.

The main differential diagnosis are cysts, cavernoma, calcifications, post-traumatic/post-inflammatory residual lesions, focal cortical dysplasia and gliosis[14].

GG may be MR captured as lesions with a combination of solid, cystic components or with calcifications. Contrast uptake may or may not be present. In such case it varies between nodular and ring features.

Usually, DNT have a multicystic morphology. 30% of cases these may have contrast uptake[15].

Hystopathology

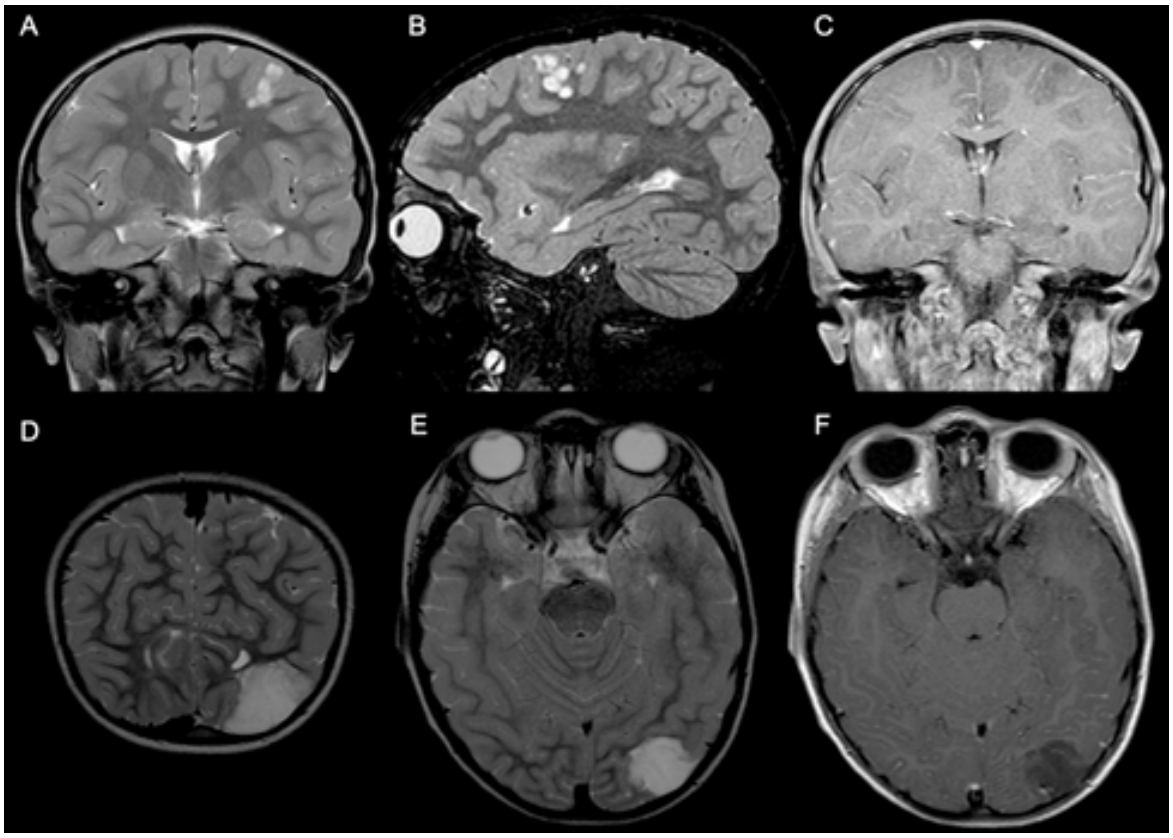
The range of patients and tumors associated to epilepsy is splitted into two big groups[8]:

1.-Low-grade neuroepithelial tumors, associated to epilepsy (LEAT), deal with glial and neuronal tumors. These are patients with early onset of epileptic seizures, who are younger than 15 years old, among them are: angiocentric glioma, ganglioglioma, isomorphic astrocytoma, DNT, pylocitic astrocytoma.

2.-Group of diffused/semi-benign/infiltrative tumors with late crisis onset, older than 15 years old, including: pleomorphic astrocytoma, oligodendroglioma, diffused astrocytoma.

GG and DNT represent 80% of LEAT[16].

Figure #1: A 5-year-old child with 1-year evolution refractory epilepsy. The imaging study shows a multinodular and vacuolated neuronal tumor (MVNT) of the left medial frontal gyrus, with a slightly-expansive focal lesion, multinodular cluster type with a high T2 signal, well circumscribed, with a cortical/subcortical location, no impregnation with the contrast medium ev. MR imaging: A) T2 coronal; B) Sagittal saturated T2; C) T1 Coronal gadolinium).
3.7-year-old girl, with a 15-month refractory epilepsy. The imaging study shows a well circumscribed parietal/occipital cortical/subcortical expansive lesion with a high T2 signal, with no impregnation with the contrast medium. The biopsy shows a Neuroepithelial Disembryoplastic Tumor (DNT). MR imaging: D) T2 coronal; E) Axial T2; F) Axial T1 gadolinium).



These tumors share some characteristics, such as: preferent location in the temporal lobe, onset age during childhood. Both may have oligodendroglial/astrocitary look-like cells, with or without any neuronal component. They may be associated to cortical dysplasia, with no mutations in IDH/ATRX genes; and lack of 1p/19q codeletion. The hardest part for diagnosing these tumors is related to high diagnostic variability among pathologists observers. As these tumors are hard to be diagnosed, based exclusively on the phenotype, the need for a diagnostic classification arises, based on histologic/inmunohistochemical and/or molecular parameters[17]. Recent publications[18][19] have classified LEAT within 3 groups: Group 1: ganglioglioma, DNT and non specified tumors, with GG predominance with BRAF V600 mutation; Group 2: DNT predominance with FGFR1 mutations; Group 3: tumors with astrocytoma characteristics, presenting MYB mutation.

During the last few years, new entities have been added within LEAT, such as multinodular/ and vacuolated neuronal tumors (MVNT) described by Huse and cols, in 2013[20]. These are subcortical/hyperintense nodular lesions in T2, compromising the subcortical white matter. The WHO has included them within the subgroup of gangliocytomas. These tumors have a low proliferation with scarce infiltrative growth. Given their histopathological and genetic characteristics, they are deemed as rather malformations of the cortical development or dysplasias[21][22]. Another recently described entity is the Low-grade neuroepithelial polymorphic juvenile tumor, described by Huse and cols, in 2017[23], which is characterized by oligodendroglial look-like cells predominance, with CD 34 marker (+).

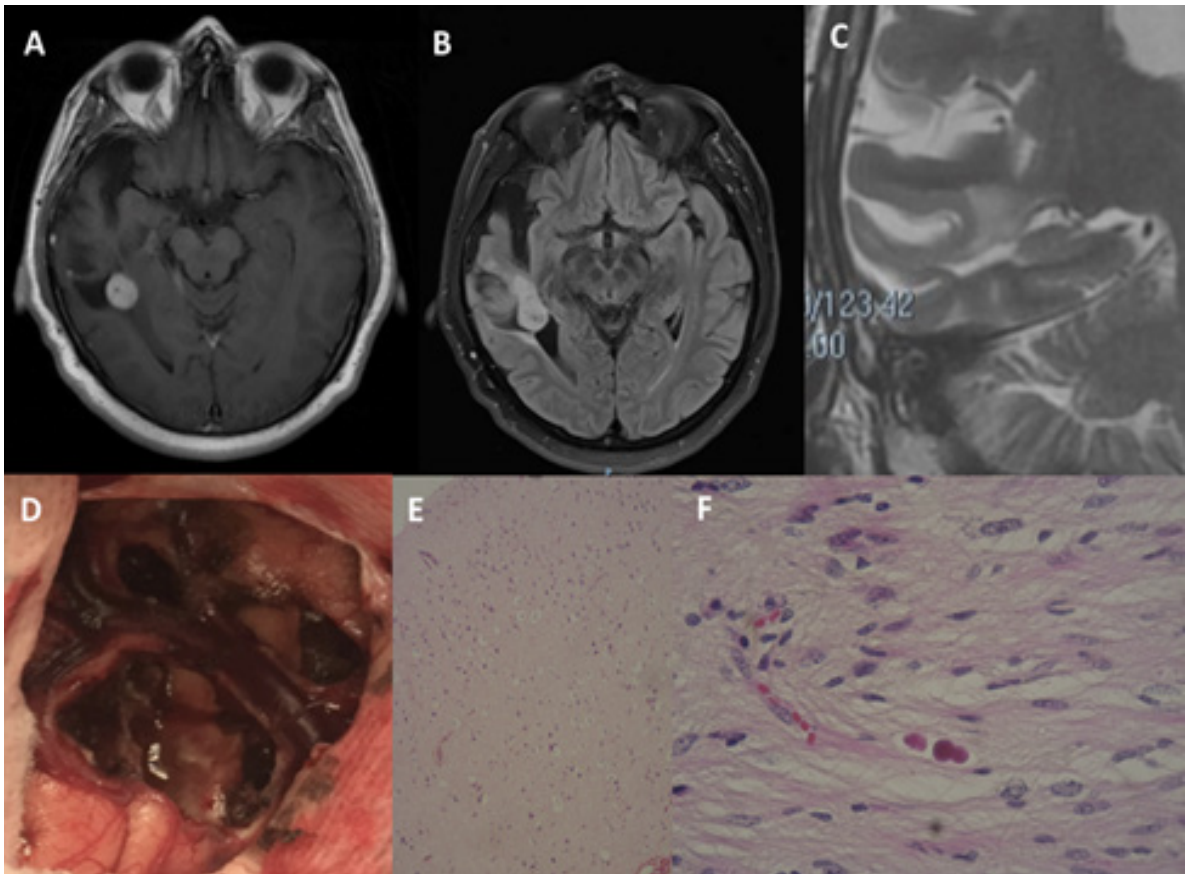
Correlation between cortical dysplasia and Low-grade neuropithelial tumors

A correlation between low-grade tumors and focal cortical dysplasia(DCF). This finding is most frequently found in the temporal lobe[8]. The correlation percentage varies in different series, Giulioni and cols[24] reported DCF in 17.7% of LEATs, from which 13% is a DCF IIIb and 2.4% a DCF IIa. In the series of Pellicia and cols[25] a correlation between tumor and DCF in 17,2% of pediatric patients and 28.1 % of adult patients was found. In 2011, after Blümcke and cols Article was published[26], DCF III was included within the new classification of cortical dysplasias, which includes correlation of DFC with another pathology. Specifically, DCF IIIb includes the correlation between DCF type I and glial and glioneuronal tumors.

The most frequent DCF imaging findings in MR are increase of cortical thickness, deletion of differentiation between white matter and grey matter, as well as increase of T2/Flair sequence signal, at a subcortical level[15]. In cortical dysplasias type II, transmantle funnel lesion is described, as extended from the cortex to the ventricle (Figure #2).

No clear definition has been made on the nature of the correlation between tumors and DCF. One hypothesis is linked to the similarities between tumor stem cells and stem cells from the central nervous system. In an adult brain it is located at a subventricular level and in the dentate gyrus. Schiyong L and cols[27], state that subventricular stem cells migrate to the DCF area, where exposure of stem cells to an anomalous microenvironment, characterized

Figure #2: 57-year-old man, with refractory epilepsy onset from childhood. The imaging study shows nodular right temporal lesion, with increased uptake in relation to the temporal right ventricular cornu. Adjacent to it, we can find a neocortical thickening area with loss of differentiation between grey matter/white matter, with high Flair/T2 signal, at the bottom of the sulcus, suggesting associated focal cortical dysplasia. MR imaging: A) Axial T1 gadolinium; B) Axial Flair; C) T2 coronal.
D) Temporal lesionectomy, with resection of focal cortical dysplasia and tumor. E) Biopsy of neocortical lesion: HE tinction with dimorphic neurons and ballonated cells, findings in agreement with DCF type II b. F) Biopsy of nodular lesion: HE tinction with a biphasic pattern of bipolar cells with Rosenthal fibers. It evolves with no epileptic seizures, after an Engel I lesionectomy.



by disturbance of the architecture, expression of aberrant proteins and genetic mutations, influences tumor genesis.

Presurgical study

Nearly 30% of patients with tumors associated to epilepsy are refractory to pharmacological management and are described as candidates to presurgical study[28][29]. The objective of presurgical study is to define the correlation between the tumor (lesion area) and the epyleptogenic zone.

The lesion is defined by using an MR study; however, we must consider that in some cases LEAT may be associated to cortical dysplasias which may not be evident in the MR. Two thirds of epileptogenic spots are deemed to be found within the tumor mass. One third is found out of it. Imaging studies are not enough to determine the relevant epileptogenic zone[13]. EGG video allows to define the epyleptogenic zone (EZ) which must be fully dried out, in order to achieve seizure-free (Engel I) during post-operative period. PET study (positron emissions tomography), is used in some Health Centers in order to locate hypometabolism zones, aimed to better locate (EZ). Even though Functional MR not always allows to accurately state the language area, it allows to predict laterality in language dominance[30][31].

An invasive study is recommended in a selected group of patients, especially when there is discrepancy between the location of the structural lesion, semiology of the crisis and the surface electroencephalographic study[13][29][30]. In the Bulacio and cols Series[32] 9,2% of the patients required an invasive study. In the Vogt and cols Series[33] from a total of 166 patients with tumors associated to epilepsy, 18% of them required a study with grids or deep electrodes. The use of subdural grids or deep electrodes or the combination of both, may be useful to identify EZ and mapping of eloquent cortex[34].

Surgical Treatment

Unlike high-grade gliomas and diffused gliomas, whose treatment is defined with oncologic criteria, the main objective of surgical treatment for LEAT patients is to control epileptic seizures.

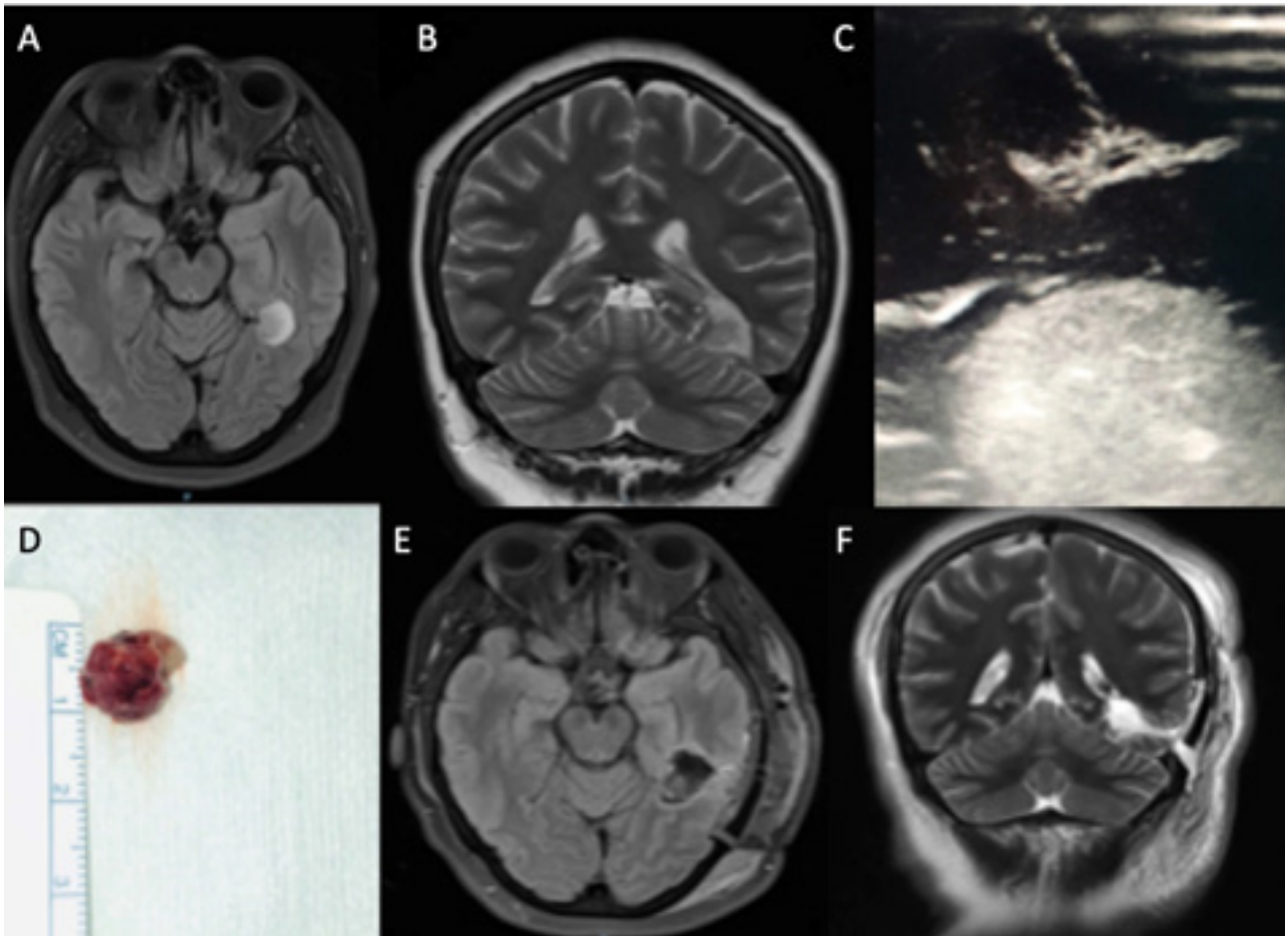
When planning surgical treatment for these tumors it is important to differentiate between temporal/extratemporal tumors. Surgical strategy most frequently described for extratemporal/neocortical temporal tumors is lesionectomy (Figure #3). In case of extratemporal tumors, we have to differentiate if these are located in an eloquent/non eloquent area. This defines the need of an invasive study or intraoperative functional cortical mapping[13].

In case of temporal lesions, we have to differentiate between neocortical temporal and temporal-mesial lesions. Taking into account the higher epileptogenicity of the temporal region, some authors state that in order to perform deeper resections, by arguing that inclusion of amygdalohippocampectomy and resection of the anterior temporal neocortex provides better results for crisis control[35][36][37].

A systematic review of Englot and cols[38] including 41 studies with a total of 1,181 patients with temporal tumors (LEAT and gliomas), extended lesionectomy plus resection of temporal-mesial structures achieved better results, in terms of crisis control in 87% of patients with Engel I post surgery. Some authors state the existence of dual pathologies (cortical dysplasia, gliosis, associated hippocampal sclerosis) may be a risk factor in post-operative crisis persistence, when no resection of the temporal-mesial structures is included[39], (Figure #4). In a series published by Grote and cols,[40] including a group of reoperated patients with temporal epilepsy, 69% of them achieved a seizure-free condition by extending the resection to a temporal lobectomy.

The main objective of epilepsy surgery is to achieve crisis control, and preserving functionality. Therefore, before defining resection of the temporal-mesial structures, among others variables, we must take into account the location of the tumor, neocortical v/s temporal-mesial, and also existence of temporal-mesial compromise, hippocampal atrophy or dual pathology en MR. Other factors to be considered are, epilepsy evolution time, neurocognitive status and memory evaluation in pre-operative[33]. Those patients with tumors compromising the temporal-mesial structures, patients with long term epilepsy, those who have signs of atrophy or temporal-mesial sclerosis, in MR are the best

Figure #3. 27-year-old woman, with a three-year evolution refractory epilepsy. EGG video: delta activity, left temporal tips. The imaging study shows a hyperintense tumoral lesion in the left fusiform gyrus. Pre-operative MR imaging: A) Axial Flair; B) T2 coronal. A lesionectomy and resection of surrounding cortex with intraoperative ecographic support is performed (C) showing hyperechogenic tumoral lesion, with well-defined edges. D) postsurgical macroscopic piece, the biopsy shows a gangliocytoma. It evolves with no Engel I post-surgery crisis. The distant imaging study of postsurgical control does not show evident tumor residues: E) Axial FLAIR, and F) T2 coronal.



candidates for temporal lobectomy or lesionectomy and temporal-mesial resection. We have to consider that in those patients with a better verbal memory performance, with tumors in the dominant hemisphere, the risk of impairment in post-operative verbal memory will be higher. While, on the other hand, performance of executive functions tends to improve or remain the same, after surgery.

Figure #5 shows a proposed surgical management scheme for temporal/extratemporal tumors.

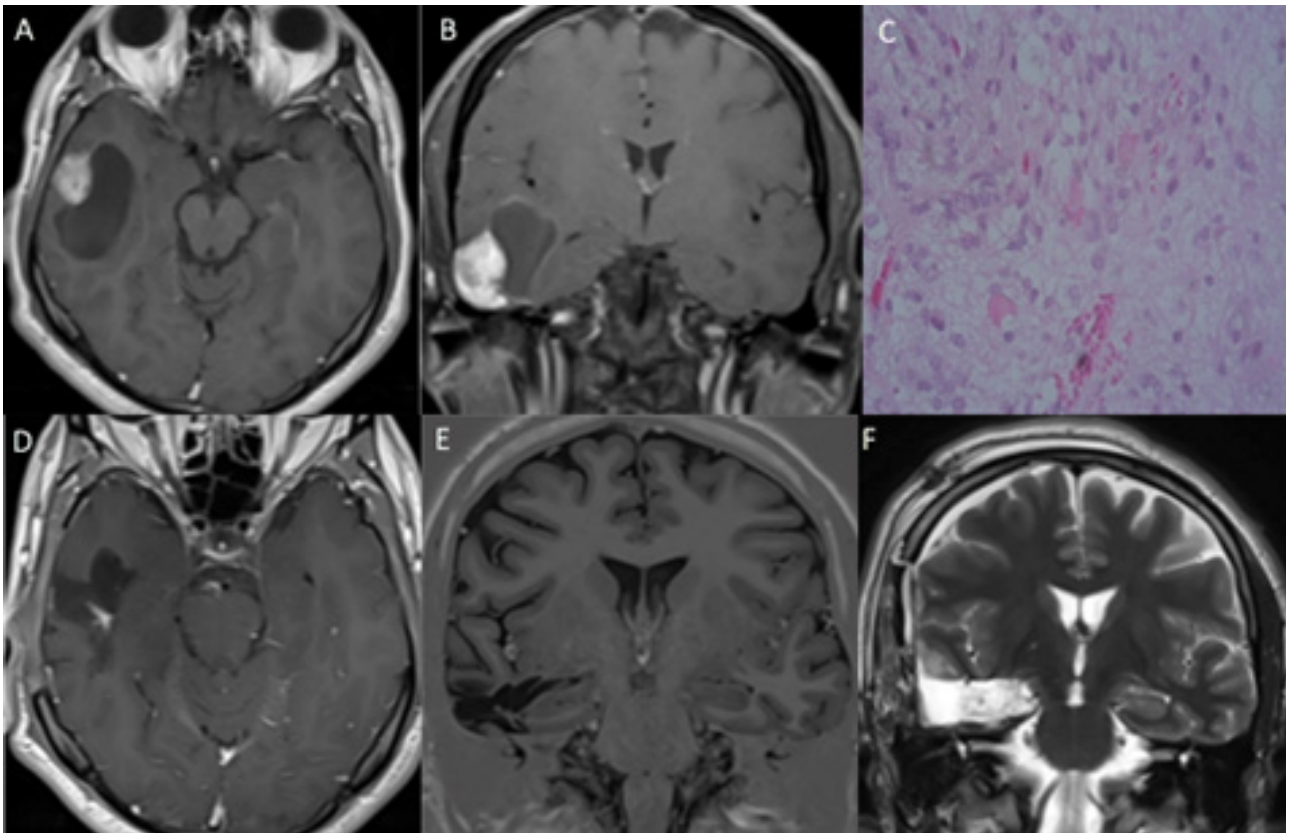
Results of Surgical Treatment and Prognostic Factors

Surgical treatment is highly likely to achieve seizure-free. In most series, a prognosis of nearly 80% of Engel I patients is achieved[41]. In a systematic review of the literature, published by Englot and cols[41], 39 studies were assessed, with 910 LEAT patients, including only gangliogliomas and DNET. 80% of patients were seizure-free, after surgery (Engel I). 20% of patients remained with crisis (Engel II-IV). Other series report 89.7% of Engel I patients, after surgery[24].

Among the factors associated to better results, in terms of crisis control are, presence of focal crises, epilepsy of less than 1 year of evolution (97% Engel I v/s 77% in patients with more than one year of evolution)[41], whole tumor resection (87% Engel I v/s 77% in partial resections)[40]. Additionally, a better crisis control in groups of non refractory patients with 98,2% Engel I[24] has been reported. In case of temporal lesions, better results have been described in lesionectomy, by adding additional cortical resection, and hippocampectomy, thus

Figure #4. 38-year-old man, with 12-year evolution refractory epilepsy, with complex partial crisis. The imaging study shows a righ-temporal solid cystic tumoral lesion, with increased uptake mural nodule. MR preoperative imaging: A) Axial T1 gadolinium; B) T1 Coronal gadolinium. A right temporal lesionectomy and post-operative MR control is performed which does not show tumor residues: D) Axial T1 gadolinium; E) coronal T1 IR. The biopsy shows (C), HE tinction: Grade II Ganglioglioma.

Post-operative evolution with partial complex persistent crisis. EGG video shows irritative right temporal activity. A new surgery with right anterior temporal lobectomy is performed: F) T2 coronal. The biopsy concludes hippocampal gliosis. It evolved with no Engel I epileptic seizures.



achieving 95% in Engel I patients.

There are series reporting lower post-operative control crisis in localized lesions within the eloquent area, achieving Engel I in 60% of all cases[29]. For pediatric patients a major pre-operative cognitive decline has been described, when there is a more severe evolution of epilepsy[24][41].

DISCUSSION

Surgery Objectives

Considering high epileptogenicity, a usual poor control of the crisis, using pharmacological management[15] and the benign condition of most of these tumors, the main objective of surgery is to release these patients from epileptic seizures. In order to achieve this goal, it is necessary to define the epyleptogenic zone, by means of a presurgical study. A noninvasive study is enough in most cases. Invasive study (Phase II) is restricted to cases where no consistent correlation is stated between the tumor and the epyleptogenic zone or in localized lesions within the eloquent area[29][32][33].

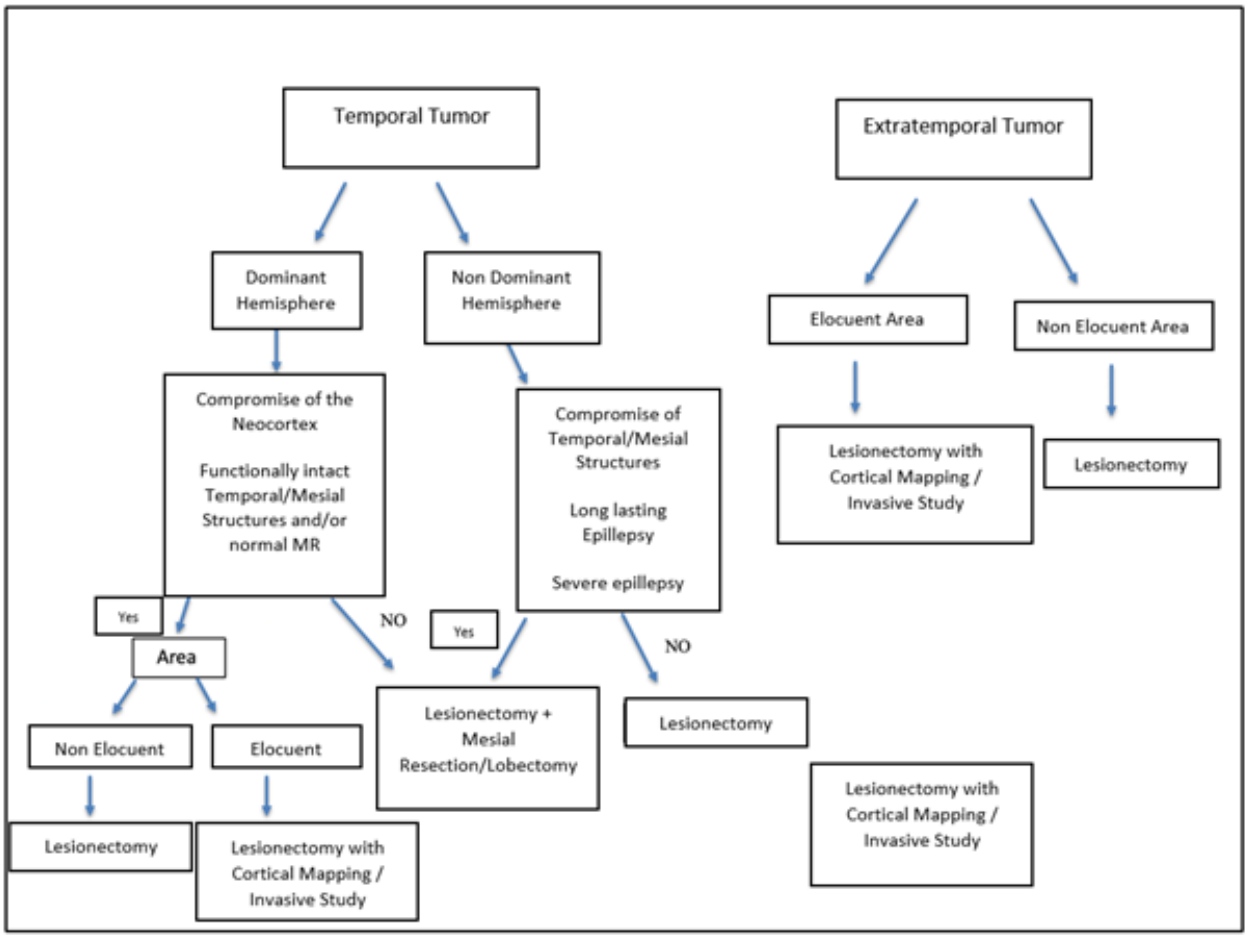
Importance of Progress in Histopathological Studies

LEATs include a range of low-grade tumors with morphological similarities; therefore, it is not enough to perform a phenotypic study to classify them; it is, additionally, necessary to perform a molecular study as done with gliomas. During the last few years new markers have been developed which have allowed to identify these tumors more accurately[8][42].

Surgical treatment

Even though there is an agreement that full resection of the tumor is correlated to better re-

Figure #5. Proposed surgical management scheme for low-grade neuroepithelial tumors, associated to epilepsy.



sults, surgical strategies vary among various authors[24][28][30][41][42]. When managing this pathology, it is necessary to differentiate between temporal and extratemporal lesions. In case of extratemporal and temporal-lateral lesions the most frequent conduct is lesionectomy[15]. Some authors suggest, additionally, to dry out a portion of 0.5 to 1 cm of cerebral cortex, as there is evidence that the cortex located between the tumor and the normal brain tissue is disturbed, becoming part of the epyleptogenic zone[28]. In lesion located in the eloquent area, it is necessary to perform an invasive study in order to confirm the correlation among tumor, epyleptogenic zone and the eloquent functional area. In these cases, another alternative aimed to delimiting the motor-eloquent/sensorial or language area is the cortical intraoperative functional mapping, even with a vigil patient, in order to preserve functionality. Regarding use of intraoperative electrocorticography there is a controversy regarding achievement of better results in terms of crisis control[13][24][29][42].

Temporal tumors may be classified into two big groups, neocortical or temporal-mesial. In case of neocortical-temporal lesions in non-eloquent areas the most common manifestation is lesionectomy. However, there are authors reporting better crisis control with wider resections including hippocampectomy, even though there is no temporal-mesial compromise. The reason of this conduct is development of secondary epileptogenesis within temporal-mesial structures, in the context of chronic epilepsy[38][43]. That is why we must consider resection of temporal-mesial structures in patients with persisting crisis, despite a full temporary lesionectomy.

In case of tumors compromising the temporal-mesial region, there is a higher consensus in the need to include temporal-mesial resection or perform a temporal anterior lobectomy. The

latter, considering the epileptogenic role assigned to the temporal pole in temporal-mesial epilepsy[15].

It is fundamental to take into account the pre-operative cognitive status and verbal memory of the patient, especially in dominant hemisphere lesions, in order to define risks[13][33]. Other aspects to take into account are epilepsy evolution time and hippocampus compromise in MR.

Prognostic Factors

Among other factors associated to better prognosis on post-operative crisis control, are full resection of the tumor, temporal epilepsy, shorter evolution period of the epilepsy, and non refractory patients. For pediatric patients this has been executed by means of pre-operative neuropsychological evaluation. In the groups of patients with a longer evolution epilepsy (more than 2 years of evolution) a deeper cognitive decline appears, compared with groups with a shorter evolution period[24]. In the published series, the latent period between crisis onset and surgery is 11.8 to 13.7 years[3][30]. Given the risk of cognitive decline in time, quality of life disturbance etc., it is better to perform early surgical treatment[44][45].

CONCLUSIONS

Low-grade neuroepithelial tumors associated to epilepsy are benign highly-epileptogenic lesions, with crisis onset during youth. Therefore, its therapeutic approach must be addressed holistically, including into the analysis, not only the lesion, but also an epilepsy surgery evaluation, which requires a proper pre-operative study in order to accurately determine the relevant epyleptogenic zone. Likewise, advance in use of molecular markers have allowed to perform a more accurate histopathological diagnosis, as because of the morphologic similarity of these tumors, it is hard to make a diagnosis, based on the phenotype only.

Surgical treatment provides a good chance to release patients from epileptic seizures, thus improving their quality of life. Additionally, it may offer the possibility to reduce or eliminate FAEs, in the long term.

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