Annex to the application for doctoral study

Charles University – Second Faculty of Medicine

Applicant's title, first name and last name:

Doctoral study programme:

Proposed topic of the dissertation (annotation):

Long – Term Epilepsy Associated Tumors: Electroclinical and Genetic Correlations

Introduction

Long-term Epilepsy Associated Tumors (LEATs) are low-grade slow-growing brain tumors with a high incidence of pharmacoresistant epilepsy. LEATs include a broad spectrum of glial and glioneuronal types of tumors, among which the most frequent are dysembryoplastic neuroepithelial tumors (DNET) and gangliogliomas (GG). Other types of LEATs are pleomorphic xantoastrocytomas, angiocentric gliomas, papillar glioneuronal tumors, extraventricular neurocytomas and tumors with hybrid characteristics. LEATs can be present in combination with other structural pathological findings, such as focal cortical dysplasia and hippocampal sclerosis.

Epilepsy surgery represents a gold-standard treatment for patients with LEATs and drug-resistant epilepsy. Even though LEATs represent the second most frequent histological finding in patients who underwent epilepsy surgery worldwide, there is limited data on the relationship between patients' clinical picture and radiological, electrophysiological and molecular-genetic features. It is known that complete resection of the tumor, its localization in the temporal region and short duration of epilepsy are associated with a higher chance of post-surgical seizure freedom. However, more detailed analyses are lacking, especially those obtained from long-term intracranial EEG and intraoperative ECoG, as well as analysis of data on patients with dual pathology.

Knowledge on genetic and other biomolecular markers of LEATs in relation to epilepsy is poor at the moment. BRAF V600E mutations, overexpression of Ki-67 protein and RINT1 gene, low expression of VLGR1 and dysregulation of miR-128 expression seem to be associated with a higher risk of epilepsy in low-grade gliomas. However, these findings were

observed in small cohorts and studies on large well-described patient populations are still lacking.

Objectives and hypotheses

We aim to analyze clinical, electrophysiological, neuroimaging and molecular-genetic findings of pediatric patients who underwent epilepsy surgery in Motol Epilepsy Center, Prague.

We hypothesize (i) that patients with dual pathology are distinct from those with LEAT alone in their clinical course, electrophysiological, neuroimaging and molecular-genetic findings; (ii) that patients with LEAT display a possibly distinct set of genetic predisposing factors compared to those with other benign brain tumors; (iii) that specific electrophysiological, neuroimaging and molecular-genetic features influence patients' post-surgical clinical outcome and can be used as prognostic biomarkers.

First, we aim to find out whether distinct tumor-specific molecular-genetic findings (e.g. V600E *BRAF* variant, *FGFR1* gene fusions and others) relate to patients' post-surgical outcomes (e.g. seizure-free status, time to withdrawal of antiepileptic drugs, cognitive performance). In collaboration with the Department of Paediatric Hematology and Oncology, 2nd Faculty of Medicine and Motol University Hospital, we will perform additional advanced molecular genetic studies on blood/derived DNA to detect potential genetic predisposing markers in patients with LEAT.

Second, we want to take advantage of an extensive dataset of intraoperative electrocorticography (ECoG) studies performed in pediatric patients with LEAT and analyze whether specific electrophysiological features relate to patients' outcomes and clinical course of their epilepsy in general. We want to focus especially on patients with dual pathology (i.e. those with histopathological diagnosis of LEAT and adjacent FCD type IIIb) to detect potential distinct electrophysiological patterns in these patients compared to those with LEAT alone.

As mentioned above, these questions have not been clearly answered yet, mainly the correlations between histological findings and intracranial EEG, as well as electroclinical differences between the various types of LEATs, especially in cases of dual pathology. Apart of this, one of the most valuable contributions of this project is the characterization of genetic findings at somatic and germinal level in correlation with electroclinical aspects of the patient.

Methods

Histological findings, data from scalp and intracranial EEG, neuroimaging, neuropsychological studies and clinical history from patients who are referred to the epilepsy surgery program of the Motol Epilepsy Center are well documented in a database (cca. 80 patients at the moment + 10 more patients in the next 2-3 years). One part of the project consists in the analysis of these data and their correlations with postsurgical outcome in term of reduction/eradication of seizures and neuropsychological changes.

In collaboration with the Department of Paediatric Hematology and Oncology, 2nd Faculty of Medicine and Motol University Hospital (Michal Zápotocký, MD, PhD) and Neurogenetic Laboratory of the Department of Paediatric Neurology, 2nd Faculty of Medicine and Motol University Hospital (Barbora Beňová, MD, PhD), we plan to perform germline and somatic genetic studies (testing of blood- and brain tissue-derived DNA obtained during pre-surgical evaluation and from epilepsy surgery, respectively) and subsequently to correlate these data with the above-mentioned parameters and the post-surgical outcome.

Applicant (Gonzalo Ramos Rivera, MD) will be responsible for assessment of electrophysiological and neuroimaging studies; collection and correlation of clinical, surgical, outcome, histological and molecular-genetic data; statistical evaluation and publishing results.

Summary

In contrast to other etiologies of epilepsy (e.g. focal cortical dysplasia), the electroclinical and genetic characteristics of LEATs have not yet been sufficiently described, even though they represent the second most frequent histological finding in epilepsy surgery patients worldwide. In our project we aim to analyze the relationship between histological findings and intracranial EEG, the electroclinical differences between the various types of LEATs and the characterization of genetic findings in correlation with electroclinical picture and post-surgical outcome. A potential and long-term goal is to outline a better patient management strategy based on the pre-surgical, electrophysiological, histological and genetic data.

Bibliography

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Supervisor's consent:

Supervisor's titles, first name and last name:

Institution of the supervisor (including address):

Considered financial coverage of the research (one´s own or supervisor's grant, sponsorship, involvement of a specific institution, etc.):

Date:

Applicant's signature: Supervisor's signature: