

Epilepsy surgery and biomarkers from history to molecular imaging

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Valorisation

Valorisation

Relevance

The individual and societal burden of epilepsy is high; worldwide approximately 68 million people have been diagnosed with this chronic neurological disorder¹. It is estimated that about 100,000 epilepsy patients reside in The Netherlands²⁻⁴. Around 60% of these patients have localization-related epilepsy⁴, of which about 35% are drug-resistant⁵.

Epilepsy has a devastating influence on the life of the patients and their social environment. It still leads to stigmatization and discrimination of patients in many parts of the world, causing deterioration of their quality of life. Due to this stigma, many patients and families are reluctant to seek help and patients encounter psychosocial problems such as unemployment, poor social/personal relationships, and poor education⁶. Comorbidity is higher in drug-resistant epilepsy patients and the mortality risk is three times higher compared to healthy individuals^{7,8}. In the United States, epilepsy healthcare costs are estimated at \$ 48,000 per patient per year, but this figure is presumably higher for some subgroups due to comorbidities or drug-resistance⁹.

Since cure is currently only a reality in a small subset of patients and many patients appear resistant to drug therapy, development of treatment alternatives remains evolving. The identification of biomarkers that monitor disease progression or prevent seizure and epilepsy development (anti-ictogenesis and antiepileptogenesis) may serve as a valuable tool in this development¹⁰. In addition, these markers may identify patients who may benefit from functional neurosurgical treatment but in whom an epileptogenic focus is not recognized by current diagnostic tools.

Potential patient group for biomarker development

A patient cohort that is suitable for the development of a biomarker requires a relatively well-defined disease entity and in this case will consist of mostly young patients with (mesial) temporal lobe epilepsy (mTLE). The development of TLE after, for instance, atypical febrile seizures, can take many years. Identification of a potential biomarker for the early stage of the disease would be a preferable goal to pursue, for this may help to predict patients who are at risk for developing epilepsy. In this thesis, four chapters describe TLE patient cohorts, which have been analyzed for a potential radiological (gray-white matter abnormalities; GWMA), molecular (GABA-transporters; GATs) and genetic (single-nucleotide-polymorphisms; SNPs) biomarker.

Study output

Relevant data described in this thesis are the differential expression of GAT-1 and GAT-3, suggesting that this may serve as a molecular biomarker in TLE patients with severe versus mild hippocampal sclerosis. A novel radioligand for the GAT-1 was developed in an attempt to visualize their distribution *in vivo* and assess its applicability to be used as biomarker. However, this radioligand did not pass the blood-brain-barrier in our animal model.

Three other key outputs from the studies in this thesis were 1. the finding that temporal pole GMWA in TLE patients are not epileptogenic, 2. do not contain focal cortical dysplasia, and 3. the finding that hippocampal sclerosis-associated TLE patients with GWMA had a significantly younger age at epilepsy onset than those without GWMA. As such, it is a potential radiologic biomarker for epilepsy onset at a young age. The findings in the final study demonstrate, to our knowledge, for the first time that the CT genotype and the T allele of the SNP rs2272400 (GAT-3, SLC6A11 gene) was significantly more common in the TLE group compared with the control group even as in the TLE febrile seizure positive (FS⁺) subgroup (19%) compared with the TLE FS⁻ subgroup (2%). The definitive affirmation of this potential genetic biomarker has to be confirmed in a larger patient-control association study.

Future perspectives and research implementation

Future research may hold a study in a larger TLE patient cohort in order to demonstrate a difference in GAT expression between TLE patients with mild hippocampal sclerosis and non-neurologic controls. In case a difference in expression is detected, this may imply that GATs can be used as biomarkers, even in the initial stage of hippocampal sclerosis. Its use in the work-up of MRI-negative epilepsy patients will only be possible when the novel GAT radioligand described in this thesis, has the ability to pass the blood-brain-barrier. Future research has to address this specific topic of blood-brain-barrier passage of this novel developed radioligand and establish its ability to bind GAT.

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