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Review

Personalized translational epilepsy research — Novel approaches and future perspectives☆
Part I: Clinical and network analysis approaches

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ABSTRACT

Despite the availability of more than 15 new "antiepileptic drugs", the proportion of patients with pharmacoresistant epilepsy has remained constant at about 20–30%. Furthermore, no disease-modifying treatments shown to prevent the development of epilepsy following an initial precipitating brain injury or to reverse established epilepsy have been identified to date. This is likely in part due to the polyetiologic nature of epilepsy, which in turn requires personalized medicine approaches. Recent advances in imaging, pathology, genetics and epigenetics have led to new pathophysiological concepts and the identification of monogenic causes of epilepsy. In the context of these advances, the First International Symposium on Personalized Translational Epilepsy Research (1st ISymPTER) was held in Frankfurt on September 8, 2016, to discuss novel approaches and future perspectives for personalized translational research. These included new developments and ideas in a range of experimental and clinical areas such as deep phenotyping, quantitative brain imaging, EEG/MEG-based analysis of network dysfunction, tissue-based translational studies, innate immunity mechanisms, microRNA as treatment targets, functional characterization of genetic variants in human cell models and rodent organotypic slice cultures, personalized treatment approaches for monogenic epilepsies, blood–brain barrier dysfunction, therapeutic focal tissue modification, computational modeling for target and biomarker identification, and cost analysis in (monogenic) disease and its treatment. This report on the meeting proceedings is aimed at stimulating

☆ A review based on the 1st International Symposium on Personalized Translational Epilepsy Research, Frankfurt, Germany, September 2016.

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much needed investments of time and resources in personalized translational epilepsy research. Part I includes the clinical phenotyping and diagnostic methods, EEG network-analysis, biomarkers, and personalized treatment approaches. In Part II, experimental and translational approaches will be discussed (Bauer et al., 2017) [1].

1. Introduction

Epilepsy affects over 50 million people worldwide and is thus one of the most common chronic neurological conditions. It is characterized not only by recurrent seizures but also by a 2- to 3-fold increase in mortality, stigma, psychobehavioral comorbidity, and decreased social participation and quality of life (QoL) [2]. Epilepsy is a heterogeneous group of conditions caused by many different underlying etiologies ranging from monogenic mutations to acquired focal lesions [3]. About one-third of patients have seizures that are refractory to current medical treatment, which is mainly directed at the suppression of epileptic seizures by globally decreasing neuronal excitability but not at comorbidities or the underlying neurobiology [4]. At the moment we are not able to prevent epileptogenesis (the development of epilepsy following an initial precipitating injury such as a febrile seizure or traumatic brain injury), and there are very few disease-modifying treatments [5].

Personalized medicine in epilepsy is currently restricted to patients with pharmacorefractory focal (mostly lesional) epilepsy syndromes who are candidates for epilepsy surgery [6]. The considerable progress in neuroimaging during the past decades and the increased utilization of invasive EEG, mainly stereo-EEG (s-EEG), allows the localization of the individual epileptogenic zone and its removal, destruction, or disconnection by microsurgery and stereotactic ablation in a small but growing number of patients, resulting in decreased mortality and increases in social participation and QoL [7,8]. Epilepsy surgery also provides access to viable epileptogenic tissue allowing unique insights in the neurobiology and pathophysiology of epilepsy, including the detection of epileptogenic somatic mutations [8–11].

Currently a second revolution in diagnosis is evolving rapidly — the detection of pathogenic gene variants in an increasing number of patients affected by epileptic seizures and encephalopathy starting during the first 2 years of life ("epileptic encephalopathies") [12,13]. The identification of causative genetic variants has given us insights into the molecular pathophysiology of epilepsy (and encephalopathies) and has facilitated the identification of molecular targets for personalized treatments in affected individuals that could potentially be used in larger patient groups. There are already examples of successful treatments directed at individual molecular mechanisms such as the use of the ketogenic diet in patients with mutations of glucose transporter genes, or the repurposing of approved drugs to treat, for instance, gain of function mutations in ion channels [13].

These recent developments open new avenues to personalized translational epilepsy research. In a broader context, translational medicine has been defined by the European Society for Translational Medicine (EUSTM) as an 'interdisciplinary branch of the biomedical field supported by three main pillars: benchside, bedside and community' [14]. Major goals of translational research are given by the promotion of improvement in prevention, diagnosis, and therapies based on highly collaborative "bench-to-bedside" approaches [15,16].

Based on the "1st International Symposium on Personalized Translational Epilepsy Research" held in Frankfurt in September 2016 we explore here several approaches to personalized translational epilepsy research.

2. Comprehensive deep phenotyping as a prerequisite for personalized medicine

Personalized medicine is based on precise phenotyping that allows the identification of well-defined groups of patients that are amenable to specific treatment approaches. The recognition of relevant and treatable factors in these groups allows the development of tailored therapeutic approaches. Even with the advent of whole genome screening, the complexity of the interaction between genetic, environmental, and stochastic processes means that deep phenotyping still plays a critical role [17]. Such a comprehensive approach encompasses different levels of information ranging from clinical features up to tissue functions, metabolites, protein, and cell function pathways as well as regulatory processes including the role of mRNA [17]. As a consequence, all available evaluation methods including patient's history, clinical examination, neuropsychological tests, imaging techniques, laboratory data, as well as electrophysiological and functional tests are suitable tools during the phenotyping process. This approach is expensive and time- and resource-consuming, and data processing and interpretation are challenging. Additionally, time and developmental dependence of the underlying pathophysiological conditions during the process of epileptogenesis are notable pitfalls in this process. As deep phenotyping comprises a huge amount of data, sufficient integration of different datasets is important [18]. A database like the Human Phenotype Ontology project (HPO) combined standardized descriptions of data with a branch tree for ranking the obtained information [18,19]. In both studies, this allowed the linking of apparently different conditions by similar features and the identification of new correlations between the underlying genetic condition and the phenotypic features. The "cross-disorder" relevance of several symptoms can thereby be established, and top-down as well as bottom-up approaches can be realized. However, this promising advance represents only a first step as the included epilepsy terms in this database are insufficient to provide a phenotypic description on the level required for deep phenotyping. The more detailed characterization of each level of information and its standardization will help to develop further computational disease models of epilepsy and extensive analysis of these data.

3. Quantitative MRI techniques to define epileptogenic lesions

Malformations of cortical development (MCD), including focal cortical dysplasia (FCD), periventricular nodular heterotopia, and polymicrogyria are common causes of refractory epilepsy, and their detection is crucial for successful epilepsy surgery [3]. FCD is often characterized by hypo-, de-, or dysmyelination in the subcortical white matter, changes that cause blurring of the gray-white matter junction and mimic increased cortical thickness in T2- and T1-weighted magnetic resonance (MR) images. These changes are often subtle and hard to identify by visual evaluation of data acquired with conventional MR sequences. It is particularly difficult to define the margin between normal and pathological brain with current techniques. Furthermore, cortex overlying and adjacent to nodular periventricular heterotopia has been shown to be epileptogenic but usually looks normal on conventional MRI [20]. One promising novel approach to improve the detection and delineation of pathological tissue in patients with MCD is the acquisition of quantitative MRI (qMRI) maps in patients with MCD, optimizing contrast characteristics for instance of the gray-white matter junction.

In contrast to conventional MR techniques which are based on the acquisition of data with different contrast weighting, the goal of qMRI is the mapping of specific tissue parameters, such as the relaxation times (T1, T2, T2*) and the proton density (PD). The advantage is that these maps provide exclusive information about the respective

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