These research projects were undertaken in partial fulfillment of the requirements for the MD degree at Sackler Faculty of Medicine, Tel Aviv University in 2018–2019. They were considered the most outstanding of the graduating class

Development of Ontology for Self-limited Epilepsy with Centrotemporal Spikes and Application of Data Mining Algorithms to Identify New Subtypes

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Background: Benign rolandic epilepsy or benign childhood epilepsy with centrotemporal spikes (BCECTS) is a common childhood epileptic syndrome. The syndrome resolves in adolescence, but 1–7% of patients have an atypical presentation, some of which require aggressive medical treatment. Early treatment may prevent complications and neurocognitive deterioration. Variants include Landau-Kleffner syndrome (LKS) and electrical status epilepticus during sleep (ESES).

Objectives: To determine data driven identification of risk factors and characterization of new subtypes of BCECTS based on an ontology. To use data mining analysis and correlation between the identified groups and known clinical variants.

Methods: We conducted a retrospective cohort study comprised of 104 patients with a diagnosis of BCECTS and a minimum of 2 years of follow-up, between the years 2005 and 2017. The medical records were obtained from the epilepsy service unit of the pediatric neurology department at Dana–Dwek Hospital, Tel Aviv Sourasky Medical Center. We developed a BCECTS ontology and performed data preprocessing and analysis using the R Project for Statistical Computing (https://www.r-project.org/) and machine learning tools to identify risk factors and characterize subgroups.

Results: The ontology created a uniform and understandable infrastructure for research. With the ontology, a more precise characterization of clinical symptoms and EEG activity of BCECTS was possible. Risk factors for the development of severe atypical presentations were identified: electroencephalography (EEG) with spike wave ($P < 0.05$), EEG without evidence of left lateralization ($P < 0.05$), and EEG localization (centrotemporal, frontal, or frontotemporal) ($P < 0.01$).

Conclusions: Future use of the ontology infrastructure for expanding characterization for multicenter studies as well as future studies of the disease are needed. Identifying subgroups and adapting them to known clinical variants will enable identification of risk factors, improve prediction of disease progression, and facilitate adaptation of more accurate therapy. Early identification and frequent follow-up may have a significant impact on the prognosis of the atypical variants.

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Evaluation of the Compatibility of Electric Tumor Treating Fields with Key Anti-tumoral T-Cell Functions

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Background: Tumor treating fields (TTFields) are low-intensity, intermediate frequency electric fields that affect proliferating cells. TTFields are FDA approved for treatment of newly diagnosed and recurrent glioblastoma. Combining TTFields with immunotherapy is a rational approach due to their different mechanisms of action (MOA) and to the ability of TTFields to induce immunogenic cell death. Conversely, TTFields may interfere with immune functions critical for effective T-cell responses.

Objectives: To evaluate the effects of TTFields on pivotal anti-tumoral T-cell functions.

Methods: T-cells from healthy donor peripheral blood (PB) or from viably dissociated human glioblastoma samples were cultured under normal or TTFields conditions, with or without superantigen stimulation. Multiparametric flow cytometry (8-color) was used to assess T-cell responses by monitoring select pivotal functions: proliferation (CFSE), IFNγ secretion, cytotoxic degranulation (CD107a), and activation/exhaustion (PD-1). Cellular viability was assessed in a dedicated assay. A chimeric antigen receptor (CAR) T-cell-based assay directly evaluated cellular cytotoxicity.

Results: Activated PB T-cells and tumor-infiltrating T-cells (TILs) preserved all monitored anti- tumoral functions under TTFields, apart from proliferation. This finding also applied specifically to PD-1 + TILs, comprised predominantly of tumor antigen-specific cells. Activated T-cells that attempted to proliferate under TTFields demonstrated decreased viability, in line with TTField MOA. Small or no reduction in viability was found in T-cells that did not attempt to proliferate, whether activated or resting.

Conclusions: All monitored anti-tumoral T cell functions, except for proliferation, were unhindered by TTFields. Our results support further investigation into combinations of TTFields with T-cell based immunotherapeutic approaches.