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MEETING ABSTRACT

A2.10

Insights into the pathomechanism of drug-resistant epilepsies

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Background: Epilepsy is one of the most common neurological group of disorders, affecting 0.5–1% of the population worldwide, of which about one third suffers from pharmacoresistant seizures. Within these, emerging groups are the epilepsies in which seizures develop due to the development of encephalitis, so the infiltration of cells of the adaptive immune system in the central nervous system (CNS). The activation of the immune system often leads to a lowered seizure threshold [1]. Here, we analyzed the interaction of the adaptive and the innate immune system in the CNS to elucidate the role of inflammation in seizure generation in human patients. We investigated Rasmussen's encephalitis (RE), which is a prime example of T cell-mediated encephalitis with pharmacoresistante epilepsy [2,3]. RE is a fascinating condition since both seizures and inflammation only are seen in one of two hemispheres. Although the role of T cells in neurodegeneration in RE has been analysed in detail, not much is known regarding the role of the innate immune system. Moreover, the inflammatory profile of other pharmacoresistant epilepsies, such as epilepsies with cortical malformations (*i.e.* focal cortical dysplasia (FCD) type IIa and IIb, as well as tuberous sclerosis (TSC)) has not been analysed in detail.

Methods: We performed whole-genome transcriptome studies of 17 RE, 5 FCDIIa, 6 FCDIIb and 6 TSC patients and compared them to age-matched controls. We further validated our data by qPCR and immunohistochemistry.

Results: In RE, we could show a broad upregulation of inflammatory pathways, ranging from interferon signalling, to T cell receptor signalling and major histocompatibility complex (MHC)-I signalling. We could validate our data by immunohistochemical analysis of the human tissue by staining for key proteins in the inflammatory cascade, such as caspase 1, interleukin 1β, interleukin 18 and toll-like receptor 7. We could show that the innate immune system actively recruits the T cells into the CNS, where they then exert their detrimental neurodegenerative effect [4]. In FCDIIa, FCDIIb and TSC we found differentially expressed pathways pointing towards a different epigenetic profile of the three diseases compared to controls, as also recently described by Kobow *et al.* [5]. Moreover, in FCDIIa, kainate receptor signalling was significantly downregulated compared to controls. Further, in FCDIIb and TSC we found a significant upregulation of inflammatory pathways. However, compared to RE the inflammation was moderate, with MHC-I-related pathways being more upregulated in FCDIIb and MHC-II-related pathways more prominent in TSC. In histopathological evaluation of T-cell subsets we could show a significant increase of CD3+ T cells in areas of cortical malformations compared to control areas of the same patients in TSC. Further, pathways linked to oxidative stress and heavy metal processing are highly upregulated in TSC and FCDIIb. Interestingly, in all three diseases the non-protein-coding transcriptome was highly represented, most prominently the small nucleolar RNA, C/D box species, which have been shown to be involved in methylation of other RNAs and alternative splicing [6].

Discussion: We will now further deepen our analysis of the whole-genome transcriptome data, and validate the differentially expressed pathways. Moreover, we will investigate the role of the small nucleolar RNA species and if they effect the pro-epileptogenic processes. This in-depth analysis will shed light into the different pathomechanisms of drug-resistant epilepsies.

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Keywords: epilepsy, drug-resistant – whole-genome transcriptome – neuroinflammation – pathomechanisms

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