Sylvain Rheims

AUTONOMIC

Neurodevelopmental impact of epilepsy on autonomic function in Dravet Syndrome

Project Coordinator:

Sylvain Rheims, Dept. of Functional Neurology and Epileptology (Hospices Civils de Lyon and Lyon 1 University) and Lyon's Neuroscience Research Centre (INSERM U1028/CNRS UMR5292/Lyon 1 University) Lyon, France

Project Partners:

Rainer Surges, Dept. of Epileptology, University Hospital Bonn, Bonn, Germany

Stijn Verhulst, Dept. of Paediatrics and Paediatric Neurology, Antwerp University Hospital, Antwerp, Belgium

Massimo Mantegazza, Institute of Molecular and Cellular Pharmacology (IPMC, CNRS UMR7275 and University Côte d'Azur), Nice, France

Dravet syndrome (DS) is a rare and orphan genetic neurodevelopmental disease. The disease typically begins before the age of one with convulsions, and evolves into a combination of severe drug-resistant epilepsy and cognitive impairment. The risk of sudden epileptic death (SUDEP) is particularly high, regardless of the age or expression of the disease. There is no preventive treatment of SUDEP. SUDEP is a sudden and unexpected death after an epileptic seizure and is the consequence of a cardiorespiratory arrest precipitated by a seizure. However, as the genetic disease in DS can affect the heart and other vegetative functions, the relationship between the effect of the repetition of seizures and the effect of the genetic disease, per se, is poorly understood. No study has ever evaluated this in detail, and a better understanding of these relationship is needed to develop ways to prevent SUDEP and to better inform patients and their families about the risk of SUDEP.

We will study in 100 patients, by means of 48-hour video-EEG, several parameters of the cardiac rhythm and of respiration during wakefulness and sleep. We aim to analyse if the latter, especially abnormal regulation of cardiac rhythm during the night and/or occurrence of central sleep apneas are related to the age of the patients, the epilepsy duration and the frequency of the seizures. Because DS starts in children but then evolves along lifetime, it is important to conduct the study in children and in adults. The use of a mouse model is particularly important as it will allow us to verify that the cardiac and respiratory abnormalities observed in patients are indeed associated with the risk of SUDEP. Furthermore, the mice will allows us to directly test whether the cardiorespiratory disorders in DS are exclusively related to seizures or whether the genetic disease plays a role.

Our project will primarily deliver clinically relevant biomarkers of cardio-respiratory dysfunction in DS. They will then be used in preclinical studies to investigate potential therapeutic targets with the best outcome measures before being use

to design a multi-centre trial of SUDEP prevention in DS. They may also be useful for improving seizure detection devices that are increasingly used, although still insufficiently accurate for certain seizure types.