

PRESUDE project “Brainstem MRI biomarker to PREDict the risk of Sudden Unexpected Death in Epilepsy”

Institution - Service de Neurologie, CHUV, Lausanne

Goals: Sudden unexpected death in epilepsy (SUDEP) is the most devastating outcome in patients with epilepsy, typically affecting adolescents and young adults below the age of 45 with drug resistant seizures, who are otherwise in good health. In fact, SUDEP may account for up to 1/3 of all causes of non-suicidal, non-accidental sudden death in this age range. Recent progresses have pointed to the primary role of post-ictal central respiratory distress, leading to the consideration of several types of preventive interventions. However, such intervention cannot yet be tested due to the lack of effective biomarkers with which to select an enriched population at very high risk of SUDEP. The PREDUSE study aims at validating such a biomarker, based on the hypothesis that patients at very high risk of SUDEP suffer from reduced capacity of their brainstem respiratory centers to restore effective breathing in response to seizure-induced apnea, hypoxia and hypercapnia, possibly reflecting a lower than normal carbon dioxide chemoreception that could persist during the interictal period. To test this hypothesis, we will study 500 patients with refractory epilepsy at high risk of SUDEP, and 100 controls, using an optimized MRI/fMRI investigation of brainstem structure and function.

Methods: Half of the patients (250) and controls (50) will be recruited and scanned at Case Western Reserve University in Cleveland, while the other half will be recruited in Switzerland and scanned at the University Hospital in Lausanne (CHUV) using the same protocol and MRI scan. According to our best-case scenario, each of the two cohorts should allow the testing our hypothesis with appropriate statistical power, and confirm their respective findings. In the event of lower than expected SUDEP rate in the selected population, data from both centers will be pooled to reach appropriate statistical power.

The MRI/fMRI protocol includes a fMRI coupled with repeated voluntary apnea to quantify the response of brainstem respiratory centers to apnea, decreased pO₂ and increased pCO₂. Respiration, pulse oxymetry, end-tidal CO₂ and O₂, EKG, and related motion will be systematically monitored during the entire experiment.

Patients will be followed for an average of 2 years after the MRI scan. Brainstem MRI findings, and in particular breath-holding triggered BOLD activation, will be compared between patients who will die of a SUDEP during follow-up and those who will not, using a nested case-control design.

Impact: PRESUDE should provide the first biomarker able to predict a very high risk of SUDEP (i.e. > 3%/year), using a technology that could be easily implemented in clinical practice if effective.

Furthermore, the collaborative framework of this study offers major opportunities to disseminate our findings. Delineating patients at very high risk of SUDEP will allow the development of feasible clinical trials to test interventions aimed at preventing SUDEP.

In search for partners: Yes

Timeline

- September 2016:

- Project starting date

- September-December 2016:

- Consolidation of all technical and logistical aspects of the project
- Test and implementation of tasks on the available equipment
- Optimization and test of the MRI sequence where appropriate
- Ethics board and other regulatory approval
- Preparation of the clinical report form

- January 2017:

- Recruitment start date

Current status: So far 36 patients and 22 healthy controls were enrolled

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Contact: Carolina Ciumas

carolina.ciumas@chuv.ch