#5: Evidence of Seizures and Sudden Death in a Post-Malarial Model of Epilepsy

Michel Baldin, Elizabeth Palmer, Daniel E. Rico, Kevin Harvatine

It is well established, though relatively unknown, that cerebral malaria (CM) leads to epilepsy in an estimated 300,000 children per year. Mortality rates among persons with epilepsy are 2-3 times that of in developed countries, and are reported as high as six times in regions where malaria is endemic. Sudden unexplained death in epilepsy (SUDEP) serves as a major mortality risk, and is now thought to involve the interaction of seizures and cardio-respiratory failure.

We investigated mice cured of CM for evidence of epilepsy and SUDEP to identify models to both investigate the mechanisms of epileptogenesis and complex epilepsy-related phenomena and to test intervention strategies.

We investigated four murine models of CM for evidence of post-malarial epilepsy by combining mouse strains (Swiss Webster (SW), C57BL/6, CBA) and two Plasmodium-berghei (Pb) parasites (NK65 and ANKA): SWPbNK65,

SW-PbANKA, C57BL/6-PbANKA, and CBA-PbANKA. Cohorts of three-week old littermates were inoculated with infected erythrocytes, then rescued with Artesunate when they demonstrated signs of advanced CM.Animals were implanted with EEG, EMG, and ECG electrodes 14 or more days post treatment, and video-EEG monitored continuously for 1-8 months per animal.

In all model combinations studied, recurrent spontaneous seizures were observed in a large fraction (50-90%) of the animals that survived to recording. Post treatment death rates prior to implant were observed in some mixtures, with the largest rate in SWPbANKA. In these cases, death was typically accompanied by a single seizure-like behavioral event followed either by immediate death or a severe decrement in health.

All epileptic mice with ECG recordings showed significant changes in cardiac activity associated with seizures. In 80% of the seizures, a transient preictal episode of tachycardia occurred followed by ictal and late-ictal bradycardia. AV node blocks were observed ictally and post-ictally in 66% of seizures.

We have developed models of post-malarial epilepsy (PoME). In long-term chronic recordings, we observe complex interactions between seizures, heart arrhythmias, and death. These observations are consistent with pathologies of the human condition of sudden unexplained death in epilepsy(SUDEP). These models, which are induced from infection not genetic mutation, therefore provide a unique platform for the study of the mechanisms of SUDEP and models to investigate the complex interactions between seizures, cardiac and respiratory dysfunction, and SUDEP.