

Sub-clinical seizures are associated with the same degree of brain injury as clinical seizures in the hypoxic-ischemic newborn piglet.

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Perinatal hypoxia ischemia (HI) is a significant cause of death and long-term neurodevelopmental disability. Prolonged oxygen and glucose deprivation leads to excitotoxic neuronal cell injury and death; over-excitation may also manifest as seizures. The newborn brain is highly susceptible to seizures although it is unclear what role they play in HI injury. Current evaluation of neonatal seizures relies on visual recognition followed by EEG confirmation. As neonatal seizures are often sub-clinical many seizures may go undetected. While clinical seizures may abate with treatment, evidence suggests they persist as sub-clinical seizures. **Methods:** Newborn piglets (n= 31) were anaesthetised, ventilated and catheterised for monitoring and blood sampling. Hypoxia (n=27) was induced by decreasing FiO₂ to 0.04 for 30 min. EEG was continuously monitored; FiO₂ was adjusted to attain low amplitude EEG (<5 µV, LaEEG). Hypotension was induced for the final 10 min. Daily aEEG was recorded to determine seizure activity. Brain MRIs were performed on day 1 and 3 post-hypoxia to obtain ¹H-spectroscopy, T2-weighted images and diffusion-weighted images, for calculation of ADC values. At 72 h post-insult animals were euthanased and neuropathological injury analysed. **Results:** Sub-clinical seizures were recorded in 52% of piglets, clinical seizures were observed in 27% and, 22% of piglets showed no seizure activity. aEEG background in hypoxic piglets with seizures was significantly lower compared with hypoxic piglets showing no seizure activity (p<0.05). 27 piglets showed histological injury after HI which was significantly greater in animals with seizure (seizures n=21) compared to HI animals with no seizure activity (p < 0.05). There was no significant difference in degree of histological injury between piglets exhibiting clinical versus sub-clinical seizures. A significant correlation was found between aEEG background on all post-insult days and histology. Seizure piglets showed a greater degree of edema on day 1 MRI as evidenced by lower cortical ADC and higher T2 values than no seizure animals (p<0.05). On day 1 and day 3, all hypoxic animals showed significantly lower N-Acetyl aspartate (NAA)/lactate ratios when compared to controls; seizure presence further delineated this difference with seizure animals exhibiting a significantly lower NAA/lactate ratio when compared to no seizure animals. A significant correlation was found between histology and MRS values at both day 1 and day 3. **Conclusion:** Presence of seizures, regardless of type, was associated with a significantly poorer outcome. Early diagnostic evaluation of all infants with birth asphyxia using MRI and continuous EEG monitoring is critical to identify and treat HI brain injury and seizures.