Neonatal Exposure to Antiepileptic Drugs Disrupts Striatal Synaptic Development. Annals of Neurology 2012.

This is a very interesting piece of research from Georgetown University in Washington, DC, on the effects of exposure to anti-epileptic drugs (AED) during critical periods of brain development. This is a laboratory-based study on rats. The authors initially discuss how the developing brain is highly vulnerable to modifications of the molecular environment of neurons and that even transient interventions during sensitive developmental periods can have long-lasting functional consequences. In relation to AED's, they note that phenobarbital (PB) exposure during gestation or early infancy has been associated with reduced intelligence quotient and decreased regional brain volumes in humans. There is also some evidence that exposure to PB might contribute to the increased risk for neuropsychiatric disorders associated with early life seizures. Unfortunately, the interpretation of results from clinical studies is limited because of the difficulty in distinguishing the long-term effects of drug treatment from the effects associated with the underlying condition. However, despite this and other evidence, PB still remains the drug of choice in the first-line treatment of early-onset epilepsy.

In this study, the researchers look at striatal medium spiny neurons (MSN) which are a specific type of neuron found in a part of the brain called the Corpus Striatum. They play a key role in initiating and controlling movements of the body, limbs, and eyes. The authors studied the effects of PB and 2 other AED's (phenytoin and lamotrigine) on the development of MSN's in rats that were exposed to the drugs very early in life corresponding to their neonatal period. They looked at the electrical and histological effects, as well as some clinical effects.

Electrical studies – their results provide the first evidence that neonatal exposure to AED's not only stunts the development of synapse function between neurons but may also produce a neurotoxic effect on surviving neurons which may in turn affect their function.

Histological studies – these showed that the appearance of dendritic spines were subtly altered in the brains of rates treated with PB. Spine width was slightly reduced and there were also relatively more dendritic filodopia – immature spines - which may represent failure to establish synapse formation.

Clinical studies – rats were exposed to what is called a "reversal learning task" a validated test of cognitive function and behaviour. Those rats treated with PB showed impaired reversal learning compared to control rats.

The authors go on to propose a potential mechanism of action for the detrimental effects observed with these AED's which is distinct from their anti-epileptic activity. The 3 AED's studied all have this property whereas other AED's, such as Levetiracetam (Keppra) do not. The authors therefore conclude that AED's used for the first line treatment of seizures in the newborn should be selected more carefully.

Note – a very interesting study for us personally as Ellie was put on relatively high doses of phenobarbitone at the age of 5 weeks on the basis that it was a "safe" drug. When we arrived in Australia her blood levels were checked and the local lab in Adelaide contacted us in a bit of a panic as her levels were so high. The idea that some AED's used as first-line treatment in the first few months of life may actually be causing harm is something that clearly needs exploring further. The authors here make the point that although their study focused on neurons in one specific part of the brain, the AED's studied have effects across many other parts of the brain and so there is potential for more widespread changes. For a genetic condition like CDKL5, we would obviously need further studies to differentiate the effects of the drugs from the effects of the underlying mutation. Further research beckons.....