Neurocognitive Impairment and Neurotoxicity

- Entire concept centers around mammalian lab studies showing increased rates of the following when exposed to Anaesthetic agents:
  - Neuronal apoptosis
  - Inhibited neurogenesis
  - Changes in dendrite spine architecture
  - Impaired synaptogenesis
- Results in:
  - Decreased cognitive functions (IQ, psychomotor memory, attention)
  - Morbidity (Mental retardation, affective disorders)
  - Mortality (Premature death)
- Ciritical period of brain "growth spurt" from 6 months in utero until 3 years of age

- Mechanisms appear to be mediated via:
  - GABA activation (volatiles, barbiturates, propofol, benzos, chloral hydrate)
  - NMDA antagonism (ketamine, xenon and N2O)

- Proposed subcellular mechanisms:
  - Endopasmic reticulum pathway
    - Inositol triphosphate activated by Anaesthesia causing excessive Ca release.
    - Causes down regulation of mitochondrial antiapoptotic protein
    - Cytochrome C leak into cytosol
    - Activates caspase 9 and 3
    - DNA fragmentation and cell death
  - Mitochondrial pathway
    - Anaesthesia induces excessive ROS
    - Lipid perioxidation of membranes and organelles (mitochondria and ER)
    - Autophagosomes produces to destroy cell to prevent excessive Ca and Cytochrome C leak
  - Lysosome pathway
    - Activation of NADP gated Ca channels results in increased lysosomal Ca
    - Increases lysosomal and autophagosomal fusion causing neuronal self-eating

Evidence

Pre-Clinical

- 1999 – Demonstrated dose-effect of NMDA antagonism related apoptosis in rats during brain developmental window
- 2003 – Demonstrated rats exposed to Midazolam, N2O and Isoflurane had increased apoptosis and persistent learning problems later in life
- Rhesus monkey studies demonstrated apoptosis but suggested safety margins

Clinical – Retrospective

- Olmstead County Cohort – Babies from NVD vs Regional vs GA all the same. Babies with multiple anaesthetics before 4 had learning difficulties. Not extrapolatable data due to non diverse population.
- Walkman et al. – Children exposed before 24 months had more "deviant" behavior. Not statistically significant
- New York Medicaid Set – Exposed under 3 years 2.3x more likely learning difficulty. Limited study

Clinical – Ongoing

- GAS (General vs Spinal) – Comparing PGA 26 to 60 weeks. Sevo vs Regional inguinal hernia. 2 year data suggests no difference. Awaiting 5 year follow-up
- PANDA (Paediatric Anaesthesia Neurodevelopment Assessment) – Exposed sibling under 36 months vs non-exposed sibling. No statistically significant IQ differences
- SAFETOTS – International group specializing in further research in this field

Ultimately

- Enough reason for concern in animals
- Animal brains are still different
- No hard clinical evidence for Anaesthesia causing issues
- Sick kiddies have other issues (sepsis, hypoperfusion, hypoxia)
- Surgery itself has a neurohumeral respouse
- Ultimately anaesthesia is needed
- ?Vulnerability window and "safe" dosing