Relationship between Cerebrospinal Fluid Endothelin-1 and Interleukin-6 Levels in Cerebral Vasospasm after Experimental Subarachnoid Hemorrhage in the Rabbit

- Project Outline -

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Inflammatory response and occurrence of cerebral vasospasm (CVS) represent a common pathogenic pathway.

Fassbender K et al. Stroke 2000
Dumont AS et al. Neurosurgery 2003
Muroi et al. Acta Neurochir Suppl 2010
Interleukin (IL)-6

- Linked with occurrence of CVS and outcome in clinical studies
- Topic application induced CVS in animal models
- Neutralizing AB showed attenuation of CVS
  Bowmann et al. Neurosurgery 2004

Endothelin (ET)-1

- One of the primary suspect in direct development and propagation of CVS
- Randomized phase 2b trial showed decreased CVS by ET-1 Receptor Antagonist
  Mc Donald et al. Stroke 2008 (CONSCIOUS-1)
- Phase 3 trial: no significant CVS-related morbidity and all-cause mortality
- Mechanism of ET-1 release and its origin unclear

- Inflammatory response and occurrence of CVS represent a common pathogenic pathway

- ET-1 production occurs by activated leukocytes with accompanying inflammatory response

  Fassbender K et al. Stroke 2000

- IL-6 may promote CVS by the involvement of activation of inflammatory cells to produce ET-1 (??)

Objective: enlighten the relationship between SAH, Inflammatory response with IL-6 expression, ET-1 and CVS
Day 0
Baseline Angiography

Day 1
Topic IL-6 Application
Topic Carrier Application
Sham Intervention

Day 3
Follow-up Angiography
CVS present
CVS present (?)
No CVS
No CVS

Collection of CSF Samples (transclival)
Euthanasia, Perfusion Fixation, Harvesting Basilar Artery and Brain

SAH Group (n=8)  IL-6 Group (n=8)  Carrier (n=4)  Sham (n=4)

IL-6 and ET-1 ELISA

SAH Group: IL-6 ↑  ET-1 ↑  IL-6 ↑  ET-1 ↑ (?)  IL-6 ↓  ET-1 ↓  IL-6 ↓  ET-1 ↓

Post Mortem Analysis

Basilar Artery Histology:
Morphologic Vasospasm (H&E) and Lc-Infiltration (CD-4)

SAH Group: CVS ↑  Lc-Infiltration ↑  CVS ↑ (?)  Lc-Infiltration (?)  No CVS  No Lc-Infiltration  No CVS  No Lc-Infiltration

Brain (Hippocampus) Histology:
Apoptotic Neuronal Cell-Death (Cleaved Caspase-3 and Matrix Metalloprotease 9)

SAH Group: Neuronal cell-death ↑  Neuronal cell-death ↑ (?)  No Neuronal cell-death  No Neuronal cell-death
- Does IL-6 trigger ET-1 release? Correlation?

- Does IL-6 cause CVS irrespective of ET-1?
  Since ET-1 RA might be insufficient...

- Does IL-6 cause neuronal cell damage without CVS?
  CVS is not the only cause of DCI...

- Might IL-6 blocking strategies be an option?
  IL-6 RA have been validated in Rheumatoid diseases...

- Monitoring of IL-6 Levels in clinical practice?
  A point-of-care test for IL-6 is available...

*** Thank You ***