Clinical Manifestations of Gd Retention: Areas of Research Going Forward?

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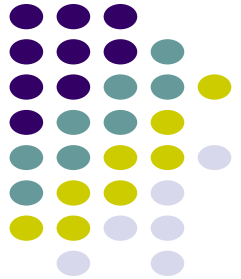
Conflicts of Interest



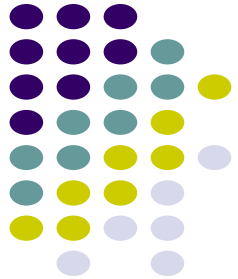
No conflicts of interest reported.

Clinical Symptomatology: Approaching Causality link to GBCA

- Adaptation of Koch's postulates is of relevance as was the case for NSF but is not yet fully evident; with parallelism providing guidance:
  - Epidemiologic / strong OR linking GBCA to all cases of NSF
  - Detection of Gd in affected tissues
  - Animal models and reproduction of disease by GBCA
  - Predisposing conditions, narrowing at risk population
  - Risk stratification based on GBCA structure and CKD stage/AKI
  - Dramatic reduction in disease incidence with limitation of exposure

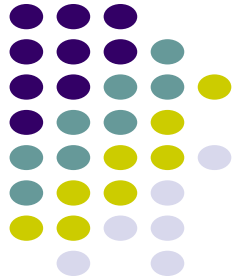
- Other relevant examples with difficult to prove associations:
  - Bisphenol A and endocrine disorders, breast cancer

Clinical Symptomatology: Gd Detection and Definition



- Quantitative detection of Gd in-vivo with functional and structures correlated on brain imaging: newer technologies
  - Gd state in tissues: exact compartment, chelated, Gd salt formation..
- Identification of predisposing factors:
  - Retrospective limited, prospective challenging but needed
  - Detailed handling of GBCA: Disposition/recovery post-dose, local and micro-environmental factors: blood-brain barrier, specific locales
- Definition of syndrome or disease like NSF:
  - Broad working/epidemiologic definition to narrower and refined one
  - Minimal set of objective verifiable elements needed
  - Characterization of symptoms, timing of evaluation, accounting for confounding by indication, pre-existent issues both as overlapping and predisposing factors
  - Consideration for subclinical findings as part of working definition

Clinical Symptomatology: Potential Approaches and Pitfalls



- Large population (exposed/non-exposed) studies: may have limitations for sub-clinical, mild or delayed manifestations
- Smaller nested cohorts with highly granular examinations and data acquisition of all cases: helpful for detectable verifiable symptoms, hypothesis generating and forming ideas for animal models, risk factors…
- Application of improved understanding of mechanisms (immunologic, toxic..), of GBCA handling and Gd deposition to designing studies.
- Documentation of spontaneous resolutions
- Documentation of improvement with removal of putative agent
- Multi-disciplinary, multi-entities approach as with NSF, transparency, early sharing of findings, open fora….