Clinical Manifestations of Gadolinium Retention: Summary of Human Data

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Gadolinium Deposition: What We Know and Don't Know
A Research Roadmap

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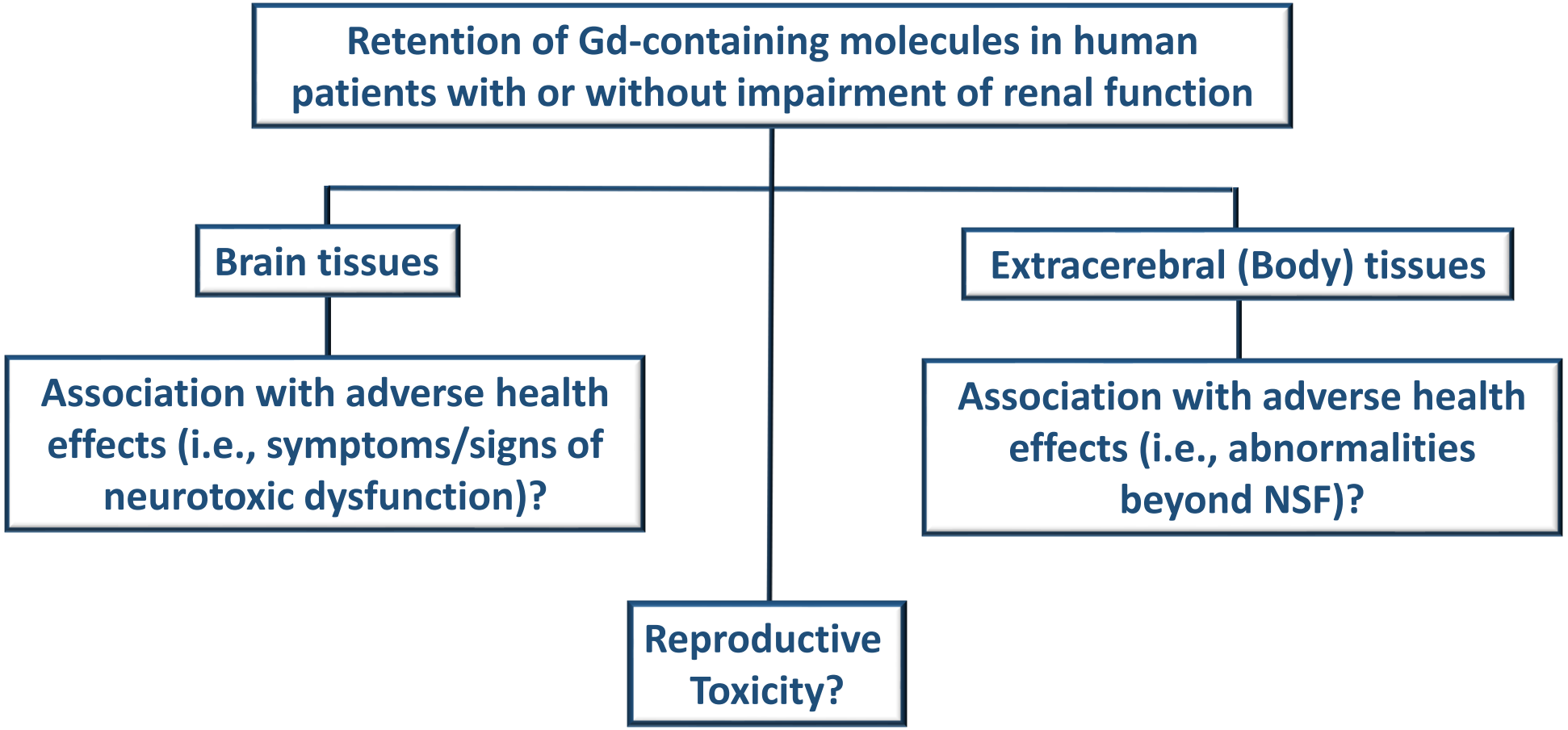
Conflicts of Interest

Bracco employee.

Presentation's Topics

- What we know
- Strengths and limitations of available evidence
- What we don't know
- Research needs

Gadolinium (Gd) Retention Following Exposure to Gadolinium-Based Contrast Agents (GBCAs) – Fundamental Questions



Gadolinium (Gd) Retention Following Exposure to Gadolinium-Based Contrast Agents (GBCAs) – Fundamental Questions

Retention of Gd-containing molecules in human patients with or without impairment of renal function

Brain tissues

Association with adverse health effects (i.e., symptoms/signs of neurotoxic dysfunction)?

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Clinical Studies Aimed at Assessing the Neurotoxic Potential of Brain Gd Retention

- **Welk et al., JAMA 2016; 316: 96-8**
  - Population-based, retrospective cohort study to assess the association between GBCA exposure and parkinsonism
- **Subset analysis of data from the Mayo Clinical Study of Aging (preliminary results reported by Dr. R. McDonald to the European Authorities and US Food and Drug Administration)**
  - Prospective, population-based cohort study to assess the association between exposure to gadodiamide (Omniscan) and impairment of cognitive function
- **Forslin et al., Am J Neuroradiol 2017; 38: 1311-16**
  - Retrospective, case-control study in patients with multiple sclerosis

Welk et al., JAMA 2016 – Methods and Results

- **Retrospective cohort study** using multiple and linked administrative databases in Ontario
- **246,557 patients >66 years of age** (median age, 73 years [interquartile range, 69-78]; **women, 54.9%**) who underwent an initial **body MRI** between April 2003 and March 2013
  - Patients with MRI to assess CNS disorders (i.e., brain or spine MRI), with prior diagnosis of parkinsonism or with prior neurosurgery were excluded
- **Primary outcome: new diagnosis of parkinsonism** based on a validated definition (accuracy: 95%) assessed from initial MRI until death (**average follow-up: 4 years**)
- **Rate of parkinsonism** per 1000 person-years of observation (95% CI):
  - **Non-Contrast MRI** (N=146,818): **2.71** (2.59-2.84)
  - **≥1 GBCA-enhanced MRIs** (N= 99,739): **3.17** (2.99-3.36)
  - **≥4 GBCA-enhanced MRI** (N= 2,446): **2.56** (1.54-4.02)
- **Relative Risk = 1.04** (0.98 – 1.09) per GBCA-enhanced MRI (P value = 0.18)

Welk et al., JAMA 2016 – Strengths and Limitations

- **In conclusion, no significant association between exposure to GBCAs and parkinsonism**
- **Well conducted population study**
  - **Large cohorts** with a similar propensity to use MRI
  - Assessment of **more than 100 baseline characteristics**
  - Involved **elderly patients**, which are **at highest risk of drug-induced parkinsonism, and a large cohort of women (female gender also a risk factor)**
- **Limitations:**
  - **Outcome likely to be more sensitive and less specific for the GBCA cohort** – actual relative risk for GBCA-enhanced MRI may be lower
  - **Relatively small number of patients exposed to GBCAs multiple times** (16,006, 16.0% of total, to 2-3 GBCA injections, and 2,446 (2.5%) to ≥ 4 GBCA injections)
  - **Follow-up limited to 4 years**
  - **Other vulnerable populations not studied** (e.g., pediatric patients)

McDonald et al., Mayo Clinical Study of Aging – Subset Analysis of Possible Neurotoxic GBCA Effect - Methods

- **The Mayo Clinical Study of Aging is a prospective, population-based, cohort study** to investigate the prevalence, incidence and risk factors for mild cognitive impairment and dementia
- **Patients enrolled in a prospective manner** since 2004
- **Extensive longitudinal clinical** (neurologic evaluation, neuropsychological testing) **and imaging** (MRI and PET/CT) **assessment at baseline and 15-month follow-up intervals**
- **Subset analysis of data from 4,261 cognitively normal study participants aged 50-89** (mean±SD: 71.9±10.7 years)
  - **1,315 patients administered ≥ 1 Omniscan doses** (742 pts received ≤4 doses, and 573 pts ≥5 doses; **median follow-up: 5.6 years**)
  - **2,946 controls** (patients never exposed to GBCAs)

McDonald et al., Mayo Clinical Study of Aging – Subset Analysis of Possible Neurotoxic GBCA Effect - Results

Neurologic Outcomes	Odds Ratio (95% CI)	P-value
Mini-mental status exam	0.95 (0.89-1.04)	0.16
Memory Z score [a]	1.04 (0.97-1.12)	0.58
Language Z score [a]	1.01 (0.98-1.05)	0.96
Attention Z score [a]	0.97 (0.92-1.02)	0.79
Visual Z score [a]	1.02 (0.98–1.05)	0.80
Unified Parkinson Disease Rating Scale (UPDRS) score:	1.01 (0.96-1.07)	0.22

[a] Raw test scores were converted to normalized *z*-scores on the basis of age, sex, and educational level

McDonald et al., Mayo Clinical Study of Aging – Subset Analysis of Possible Neurotoxic GBCA Effect - Results

- **A total of 670 (16%) of the 4261 participants progressed to mild cognitive impairment (MCI) during the study timeframe**
- **MCI rate** per 1000 person-years of observation (95% CI):
  - **Omniscan: 29.1** (25.7-31.2)
  - **Control group: 27.6** (24.9-30.4)
- **Relative risk (hazard ratio):**
  - **Omniscan exposure: 1.02** (95% CI: 0.95-1.20), p = 0.77
  - **Cumulative lifetime Omniscan dose: 0.99** (95% CI: 0.95-1.08), p = 0.85
- **In conclusion, Omniscan exposure was not a predictor of excess cognitive decline (or altered motor performance) compared to controls**

McDonald et al., Mayo Clinical Study of Aging – Subset Analysis of Possible Neurotoxic GBCA Effect – Strengths and Limitations

- **Well conducted population study**
  - **Prospective design** with subjects randomly selected from a defined population
  - **Large battery of validated neurologic and neuropsychological tests**, with most subjects examined in person
  - **MCI defined using validated criteria**, with diagnosis made by a team of experts taking into account possible confounding factors (gender, education, prior occupation, Charlson comorbidity index, alcohol use, etc.)
  - Involved **elderly patients**, which are **at higher risk of drug-induced cognitive impairment**
- **Limitations:**
  - Considering **sample size and event rates**, hazard ratios of 1.09 or higher could be detected with 80% power
  - Relatively **small number of patients exposed to GBCAs multiple times**
  - **Follow-up limited to 6 years**
  - **Other vulnerable populations not studied** (e.g., pediatric patients)

Foslin et al., Am J Neuroradiol 2017 – Methods and Results

- Retrospective longitudinal study aimed at investigating the **relationship of multiple GBCA administrations with SI increase in the DN and GP, and any association with cognitive function** in patients with multiple sclerosis (MS)
- A total of **23 patients with multiple sclerosis** and 18-year follow-up, and 23 healthy, age-/gender-matched single time point controls underwent one unenhanced MRI scan
- Patients underwent **neurological and neuropsychological evaluations** at 3 time points during the study, **at baseline, 9-year follow-up, and 18-year follow-up**
- An **increased signal intensity in the dentate nucleus was associated with lower verbal fluency scores**, which remained significant after correction for several aspects of disease severity ($\beta = -0.40$; $P = .013$)

Foslin et al., Am J Neuroradiol 2017 – Strengths and Limitations

- The strength of the study is the **long (18-yr) follow-up**
- Limitations:
  - **Small sample size**
  - **Lack of a matched MS group not exposed to GBCAs**
  - **Difficult to separate the effects of MS progression and a hypothetic effect on cognition attributed to GBCA**

Lanthanum Carbonate and Cognitive Function in Stage 5 CKD Patients – Altmann et al., Kidney International (2007) 71, 252–259

- **Prospective, randomized, controlled clinical trial** aimed at comparing long-term (2-yr) effects on cognitive function of **lanthanum carbonate vs. standard phosphate binding agents**
- **360 hemodialysis patients** randomized to **lanthanum carbonate (N=179) or standard therapy (N=181)**
- Changes in cognitive function were evaluated over time using the **Cognitive Drug Research computerized cognitive assessment system, a highly sensitive method used in drug development**
- Cognitive function deteriorated over a 2-year time period
- **Differently from what observed with aluminum hydroxide, chronic exposure to lanthanum carbonate did not adversely affect cognitive function compared with standard therapy**

Neurotoxic Potential of Gd Retention: What We Know

- **No evidence of effects on cognitive function and motor skills**
  - In elderly patients
  - Exposed to ≥1 doses of GBCAs (most frequently <4)
  - Followed up for 4-6 years
- **Chronic exposure to lanthanum not associated with adverse effects on cognitive function in hemodialysis patients**
- **Available clinical evidence consistent with absence of evidence of neurotoxicity of Gd-containing molecules observed in tissue-sample studies in human patients**

Neurotoxic Potential of Gd Retention: What We Don't Know

- **Lack of evidence re: possible effects on cognitive function and motor skills:**
  - In pediatric patients
  - Large cohort of patients exposed > 5 times to GBCAs and/or
  - Follow-up longer than 6 years
- **Possible presence of subclinical changes**
- **Possible differences among individual GBCAs**

Neurotoxic Potential of Gd Retention: Research Needs

- Well designed, properly powered prospective studies
- Study population: pediatric patients and/or patients exposed ≥5 times to GBCAs
- Comparison of neurotoxic potential of individual GBCAs
- Neurological endpoints sufficiently sensitive for detection of subclinical changes
- Proper duration of follow-up
- Minimizing bias and maximizing control over confounding factors

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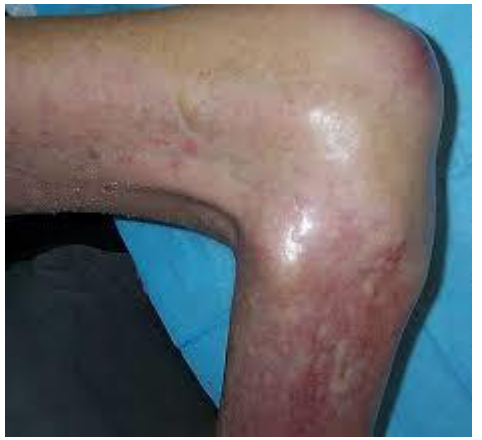
city?

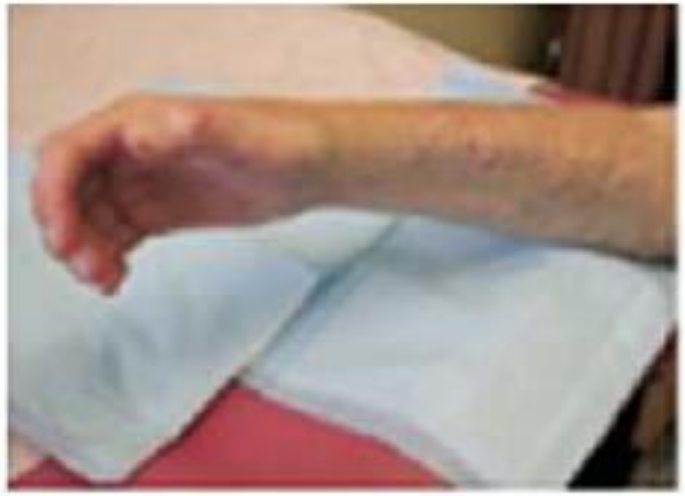
Extracerebral (Body) tissues

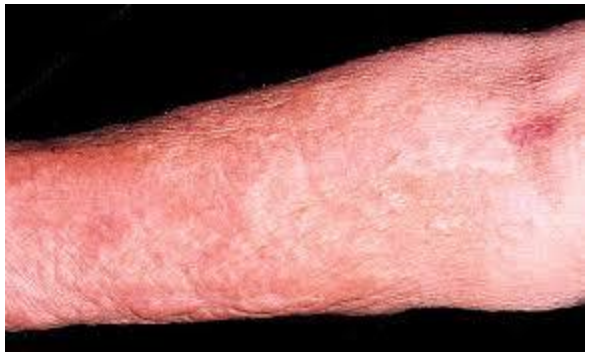
Association with adverse health effects (i.e., abnormalities beyond NSF)?

Clinical Manifestations Reported as Possibly Associated with Body Gd Retention – What We Know

- Association with NSF
- Patients with severe impairment of renal function







Clinical Manifestations Reported as Possibly Associated with Body Gd Retention – What We Don't Know

- **No evidence to understand whether there is any association between non-NSF reports of clinical adverse events and association with exposure to GBCAs**
  - **Gadolinium-Associated Plaques** [1-3]
    - 3 cases of pruritic or asymptomatic erythematous plaques, 0.5 to 2.5 cm in diameter (2 patients with normal renal function
    - At histopathology: eosinophilic, collagenous, Gd-containing round or ovoid bodies (sclerotic bodies) in various stages of calcification
  - **A total of 139 case reports of markedly heterogeneous symptoms**
    - Onset: hours, days or weeks after even a single injection or linear or macrocyclic GBCAs (mostly within the first 24 hrs; almost always within 6 weeks)
    - Lasting for > 4 weeks (range: 1 month – 9 years; median: 5 months)

1. Bhawan et al., J Cutan Pathol 2013; 40:812-817; 2. Gathings et al, JAMA Dermatol 2015; 151:316-319; 3. Bandino et al., JAMA Dermatol 2018; 154: 105-6 4. FDA Briefing Document for Medical Imaging Advisory Committee, September 8, 2017, pages 12-42. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/UCM572848.pdf.

Clinical Manifestations Reported as Possibly Associated with Body Gd Retention – Considerations for Clinical Investigations [1]

- **Patient population – not easy to define**
  - Late-onset, non-NSF adverse events have been reported in all categories of subjects [1]
  - No risk factors ever reported (type and extent of GBCA exposure included)
- **Design**
  - Prospective, cohort study of exposed and non-exposed subjects (e.g., subjects undergoing unenhanced MRI)
- **Initial Follow-up**
  - 6 weeks (or until onset of symptoms, whichever comes first)

1. FDA Briefing Document for Medical Imaging Advisory Committee, September 8, 2017, pages 12-42. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/UCM572848.pdf. Accessed Jan 21, 2017

Clinical Manifestations Reported as Possibly Associated with Body Gd Retention – Considerations for Clinical Investigations [2]

- **Endpoints**
  - All tissues could potentially be affected, with the potential of a large number of symptoms/adverse events (if any)
    - The available reports had a median of 7 adverse events/patient (range 1-39), with some clustering around certain clinical categories of adverse events (pain syndromes, neurological, cutaneous, and musculoskeletal) [1]
    - Clinical investigations should include endpoints more sensitive than NSF for potential body reactions
- **Sample size – difficult to estimate**
  - Frequency of possible late-onset, non-NSF adverse events is unknown

1. FDA Briefing Document for Medical Imaging Advisory Committee, September 8, 2017, pages 12-42. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/UCM572848.pdf. Accessed Jan 21, 2017