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

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)?

Extracerebral (Body) tissues
- Association with adverse health effects (i.e., abnormalities beyond NSF)?

Reproductive Toxicity?
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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)
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)
## Neurologic Outcomes

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

*a* Raw test scores were converted to normalized z-scores on the basis of age, sex, and educational level
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)
• 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 (β = -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

- 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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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)

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)

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