Who's Afraid of Gadolinium?

A Review of the Evidence

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MAYO CLINIC

Disclosures

Industry or Professional Relations

- GE Healthcare – Scientific Advisor & Investigator-Initiated Research Support
- ACR Committee Member – Drugs and Contrast Media

Off Label Use

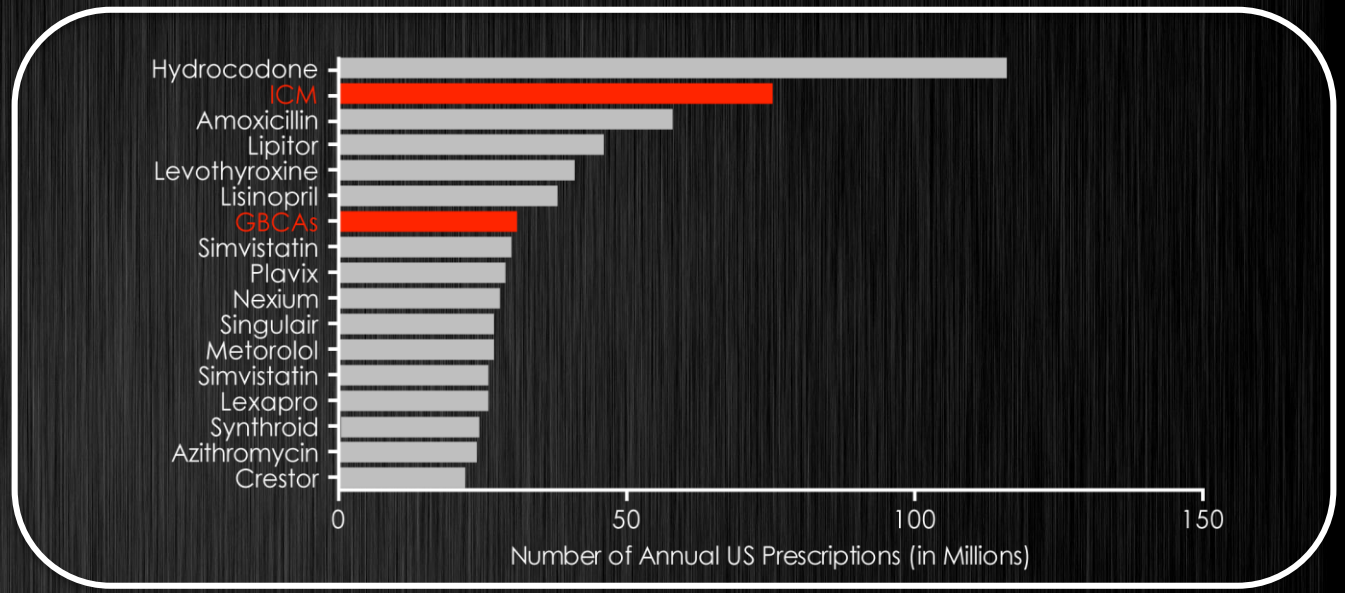
- None

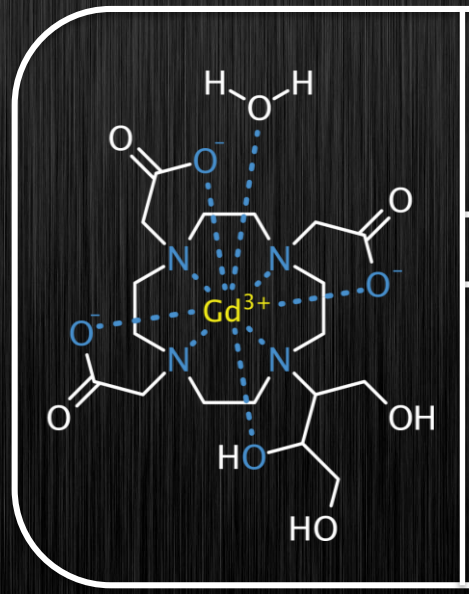
Talk Outline

1. GBCA and Gadolinium Retention Background
2. Macrocyclic vs. Linear GBCAs
3. Are Gadolinium Deposits Toxic?
4. Are Gadolinium Deposits Clinically Relevant?
5. Why Not Just Use Macrocyclic GBCAs?

GBCA Safety

- Over 450 million GBCA doses administered worldwide!
- Adverse effects can be severe, and even life altering/ending.
- We have an obligation to mold our practice patterns to the safety profile of these agents and to take steps to minimize harm to patients.





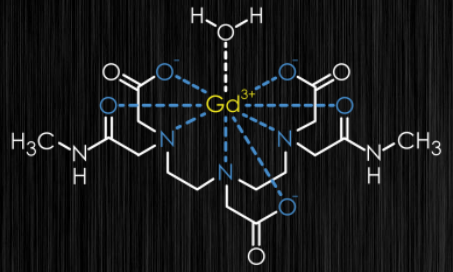
GBCA Enhanced Scans/Year: 40 million
Cumulative doses: 450 million

Side Effect	Frequency	Cases / year
Mild Rxn	0.1%	40,000
Mod. Rxn	0.01%	4,000
Severe Rxn	0.001%	400
NSF	0.00001%*	4-40

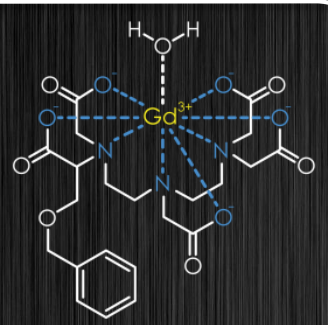
Gadolinium-Based Contrast Agents (GBCAs)

Available as of 2020

Linear GBCAs

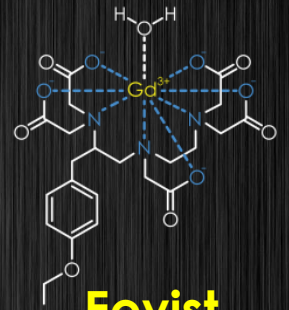


Omniscan
(gadodiamide)
GE Healthcare
1993



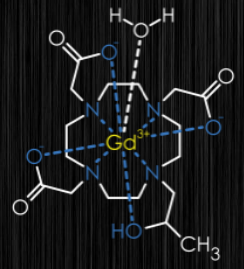
Multihance
(gadobenate dimeglumine)
Bracco
2004

Specialty GBCAs

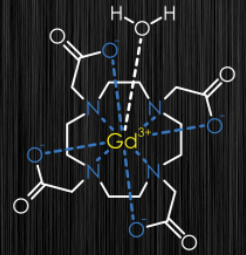


Eovist
(gadoxetate disodium)
Bayer Healthcare
2008

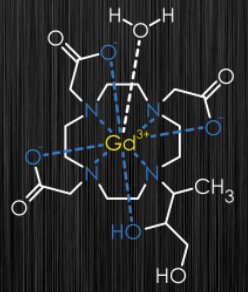
Macrocyclic GBCAs



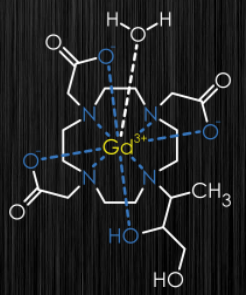
Prohance
(gadoteridol)
Bracco
1992



Gadavist
(gadobutrol)
Bayer Healthcare
2011



Dotarem
(gadoterate meglumine)
Guerbet
2013



Clariscan
(gadoterate meglumine)
GE Healthcare
2019

T1 Hyperintensity and Gd Retention

ORIGINAL RESEARCH ■ NEURORADIOLOGY

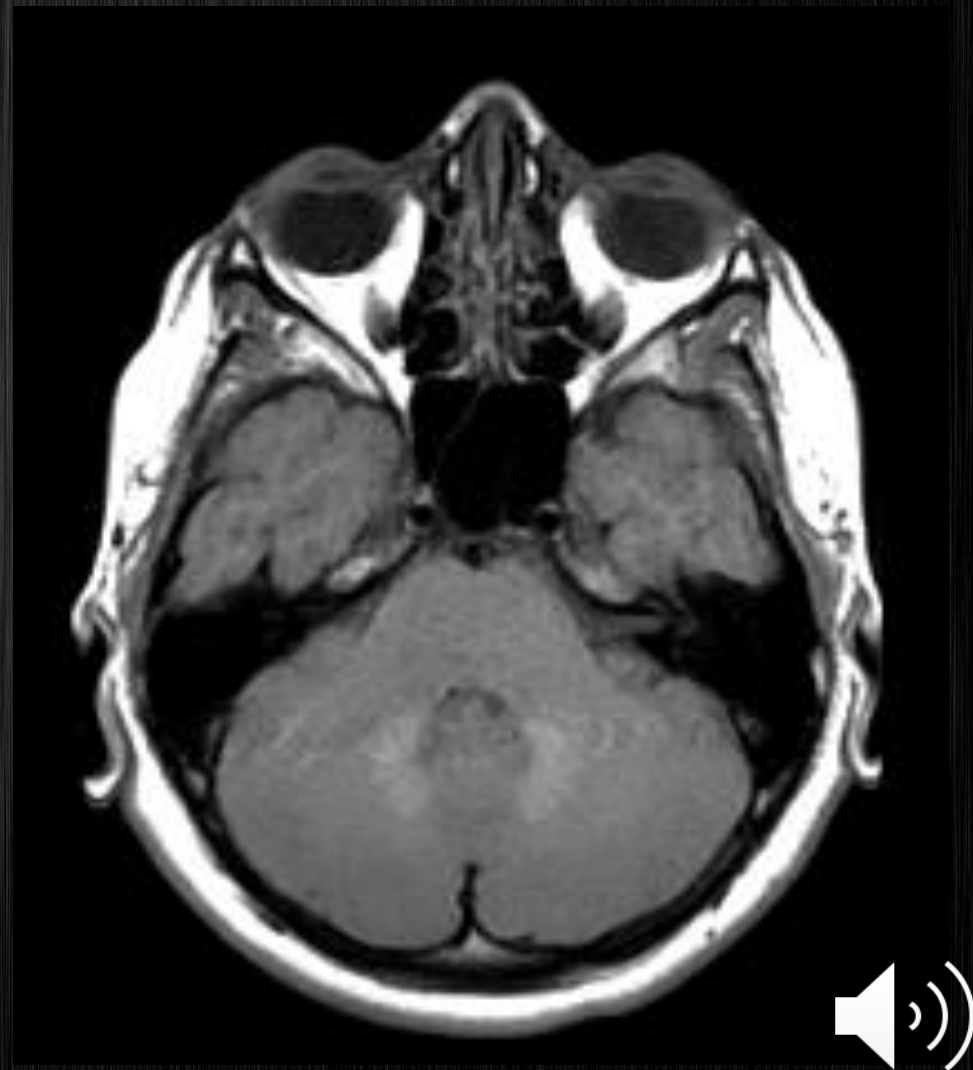
High Signal Intensity in the Dentate Nucleus and Globus Pallidus on Unenhanced T1-weighted MR Images: Relationship with Increasing Cumulative Dose of a Gadolinium-based Contrast Material[1]

Tomonori Kanda, MD, PhD
Kazunari Ishii, MD, PhD
Hiroki Kawaguchi, MD
Kazuhiro Kitajima, MD, PhD
Daisuke Takenaka, MD, PhD

Purpose: To explore any correlation between the number of previous gadolinium-based contrast material administrations and high signal intensity (SI) in the dentate nucleus and globus pallidus on unenhanced T1-weighted magnetic resonance (MR) images.

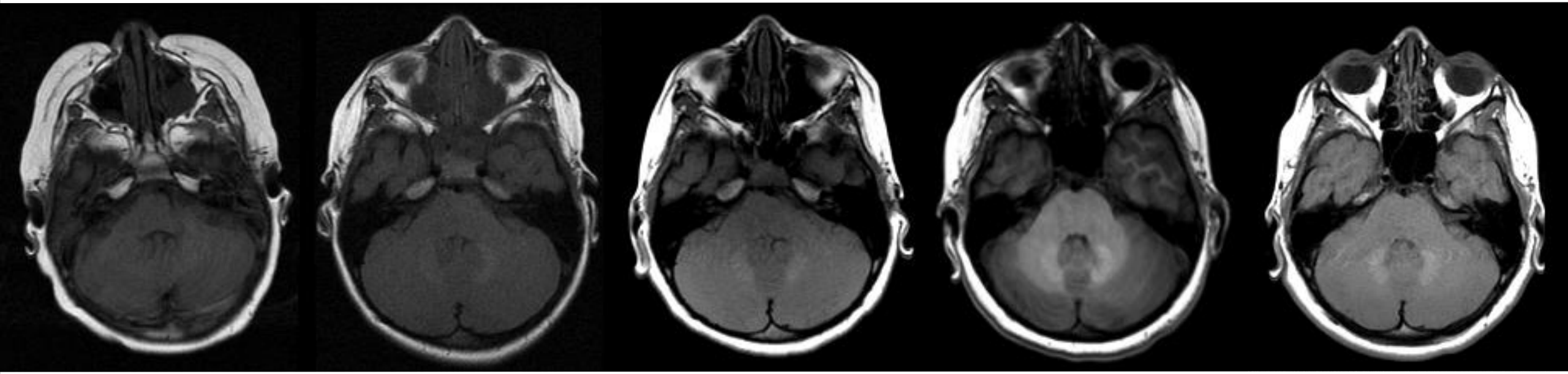
Materials and Methods: The institutional review board approved this study, waiving the requirement to obtain written informed consent. A group of 381 consecutive patients who had undergone brain MR imaging was identified for

Radiology



Intracranial Gadolinium Retention

PRELIMINARY MR EVIDENCE



3/8/2004	3/17/2006	4/16/2008	8/11/2011	3/4/2014
1st scan	7th scan	13th scan	19th scan	26th scan

Intracranial GBCA Retention

STUDY DESIGN / METHODS

STUDY INCLUSION/EXCLUSION CRITERIA

1) Underwent 4+ Gd-enhanced or 1+ unenhanced brain MRIs
2) Had appropriate pre-contrast T1W sequences
3) Underwent autopsy with antemortem consent

Contrast Exposed Group: N = 13
Non-contrast Group: N = 10

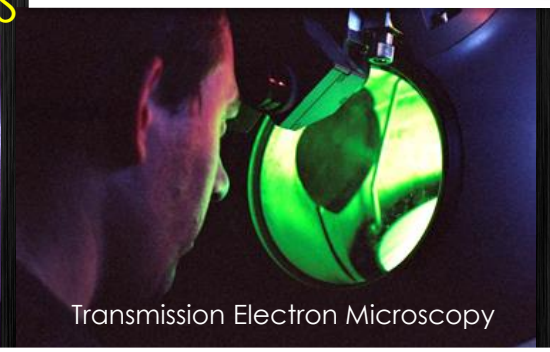
EMR SEARCH

1) Demographics
2) Comorbidities
3) Labs at time of MRI

eGFR, Alk Phos, AST, Bilirubin

TISSUE ANALYSIS

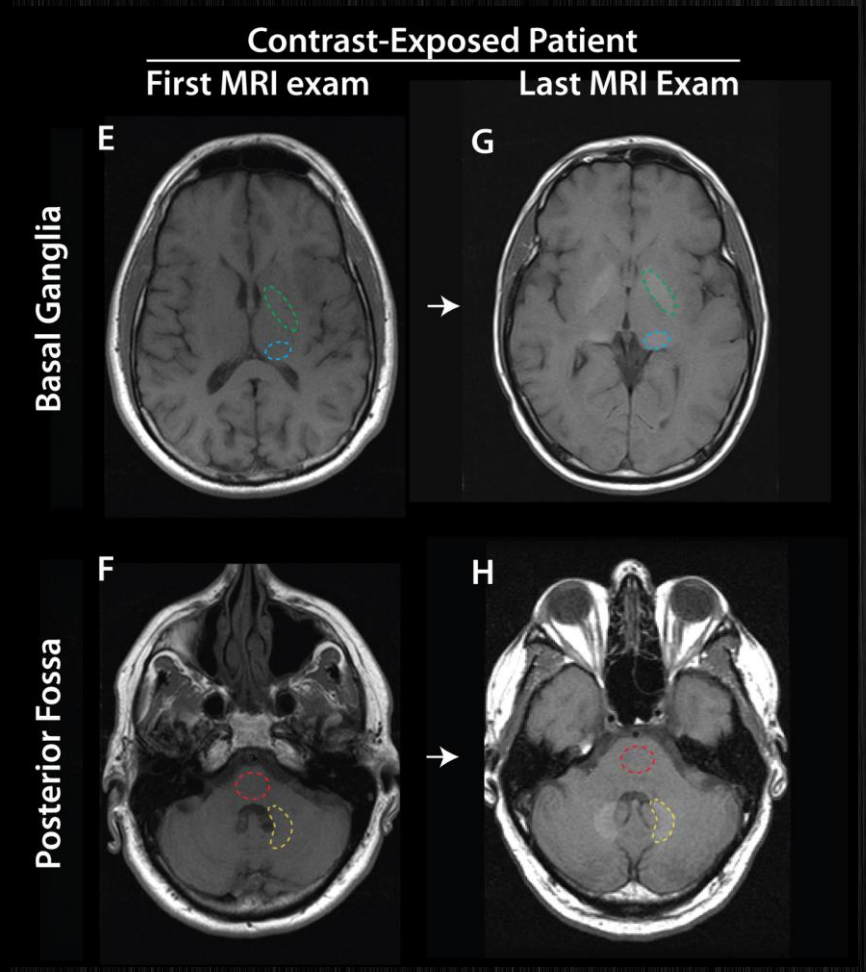

ICP-Mass Spectrometry

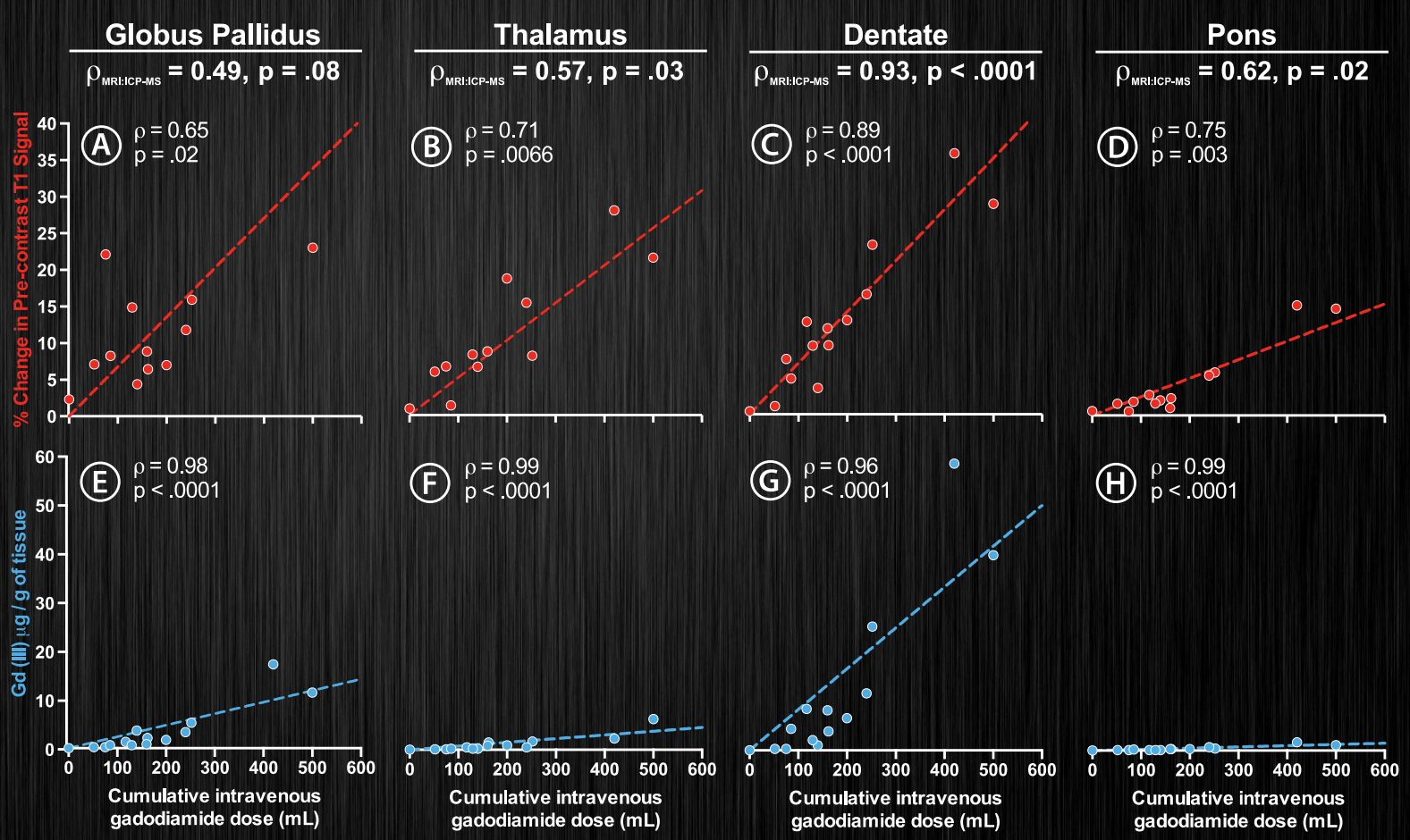

Transmission Electron Microscopy


Light Microscopy

Intracranial Gadolinium Retention

CONFIRMATORY ICP-MS EVIDENCE





McDonald et al, Radiology 2015

Intracranial Gadolinium Retention

CONFIRMATORY TEM EVIDENCE

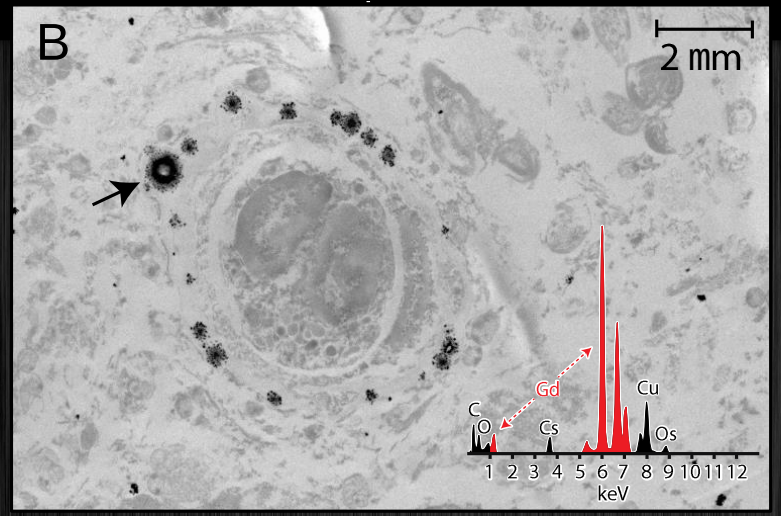
Control Patient

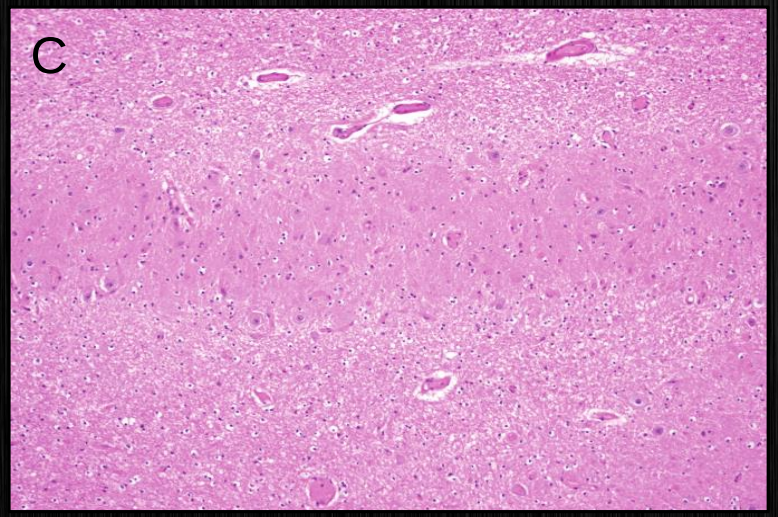
Gadolinium Exposed Patient

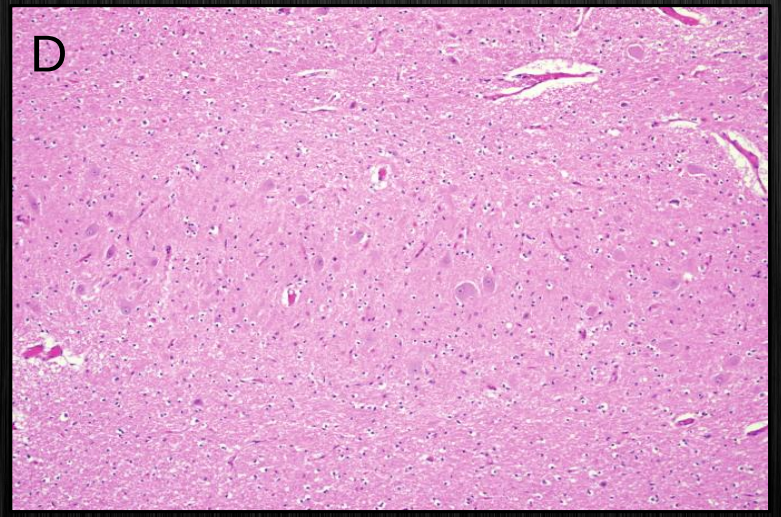
Gadolinium Exposed Patient

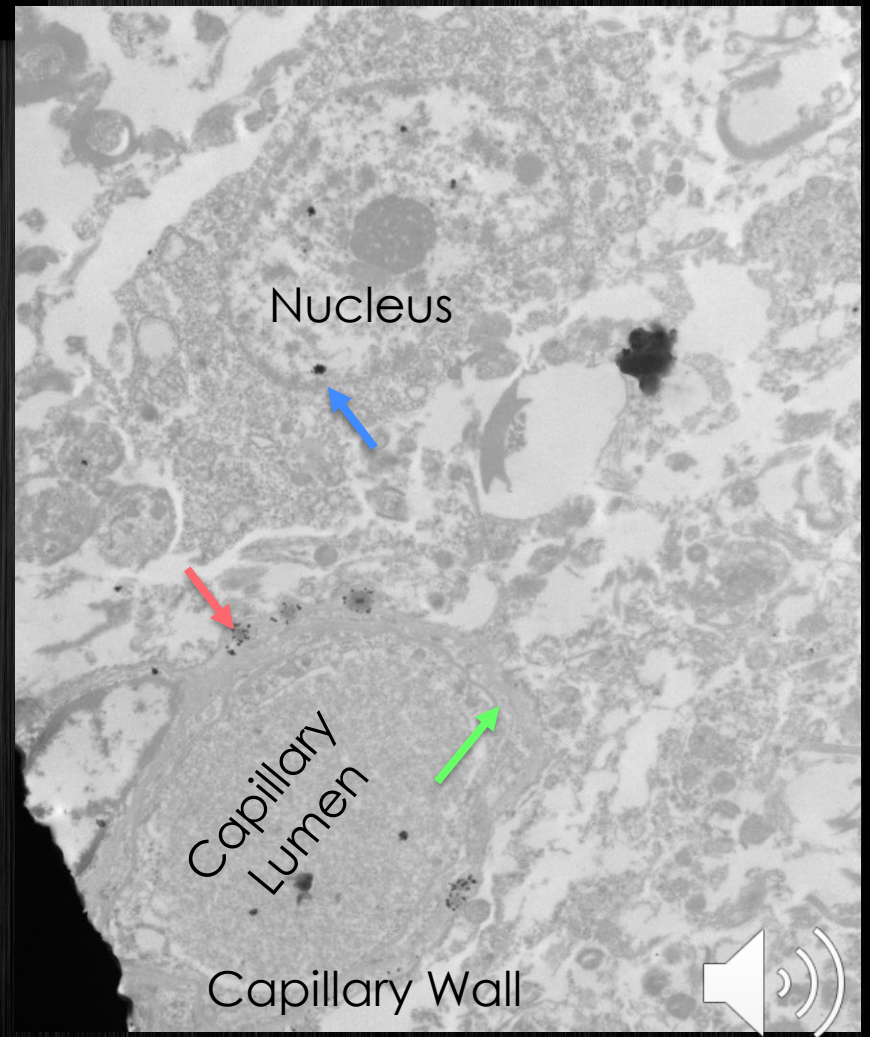
TEM

Light Microscopy









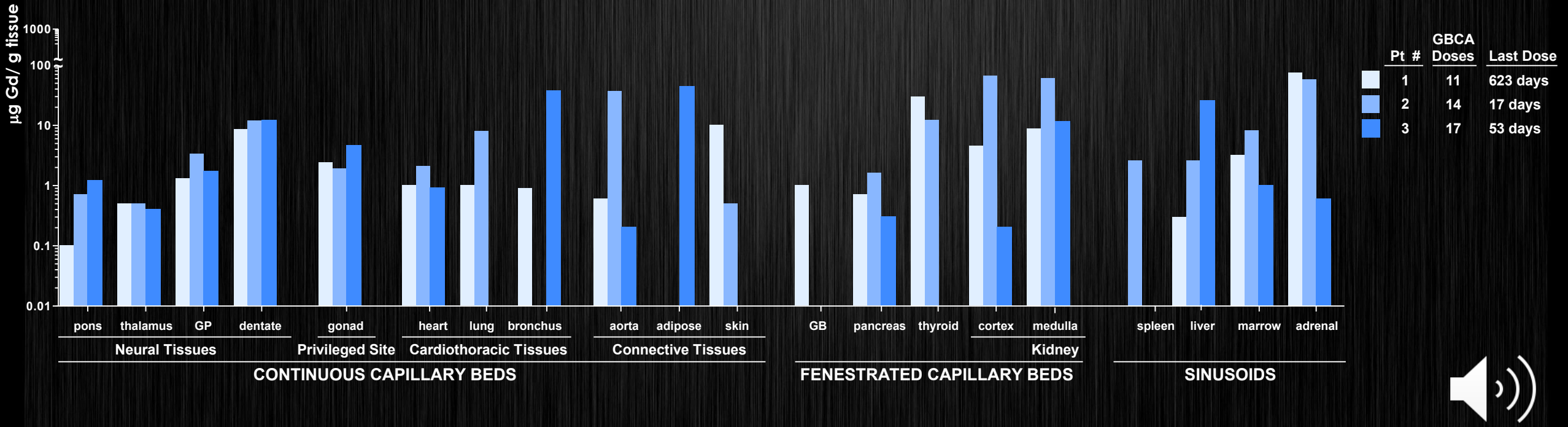
McDonald et al, Radiology 2015

Intracranial Gadolinium Retention

HOW WIDESPREAD IS THIS PHENOMENON?

B

- Gd retention was observed in patients exposed to linear and macrocylic GBCAs.
- Gd appears to be retained in nearly every tissue!

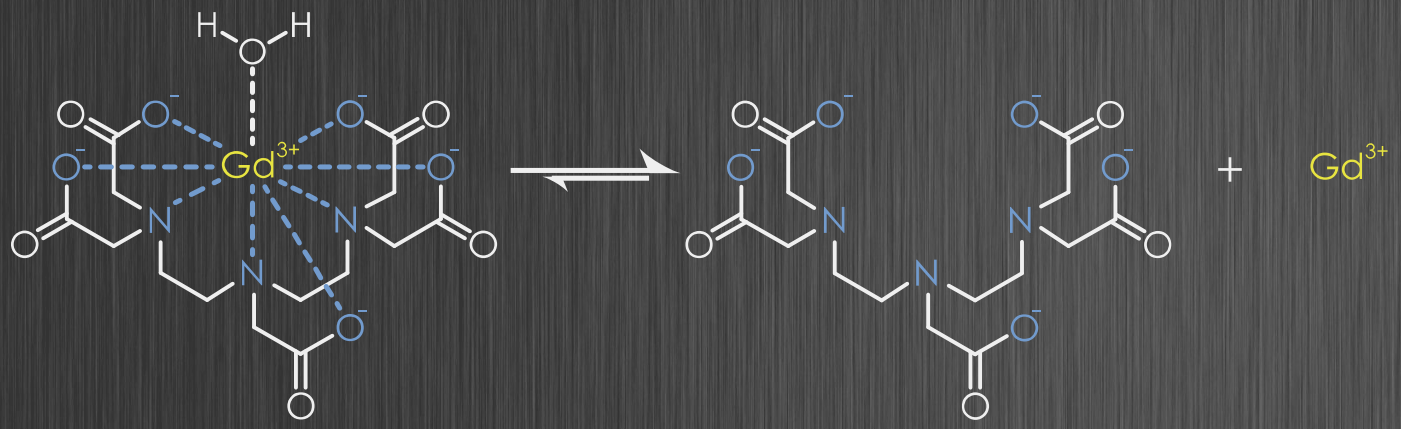


McDonald et al, Unpublished data

Macrocyclic vs. Linear GBCAs

CHEMICAL JUSTIFICATION

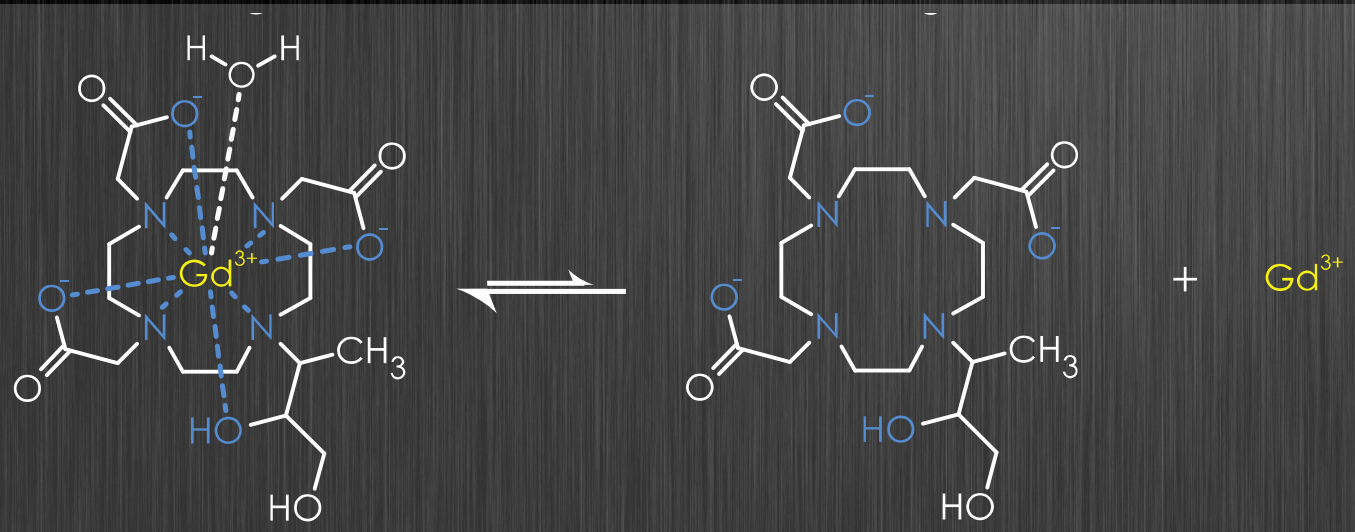
Linear GBCA



Weaker Gd: Chelate Binding

More Likely to Spend Time in Dissociated State

Macrocyclic GBCA

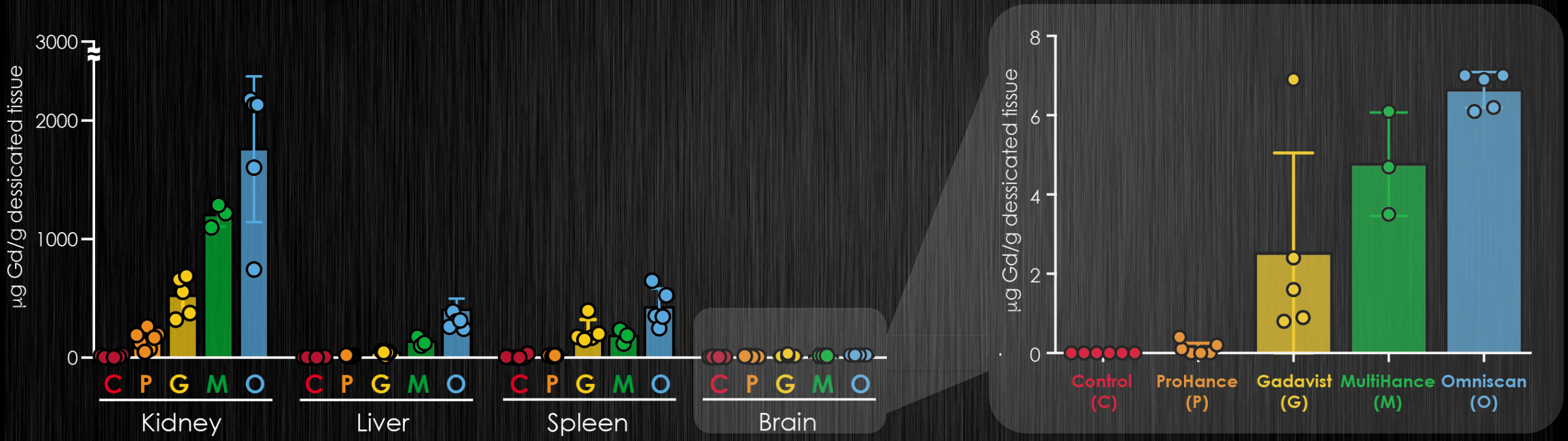


Stronger Gd: Chelate Binding

Less Likely to Spend Time in Dissociated State

Macrocyclic vs. Linear GBCAs

PRECLINICAL MODEL OF GD DEPOSITION

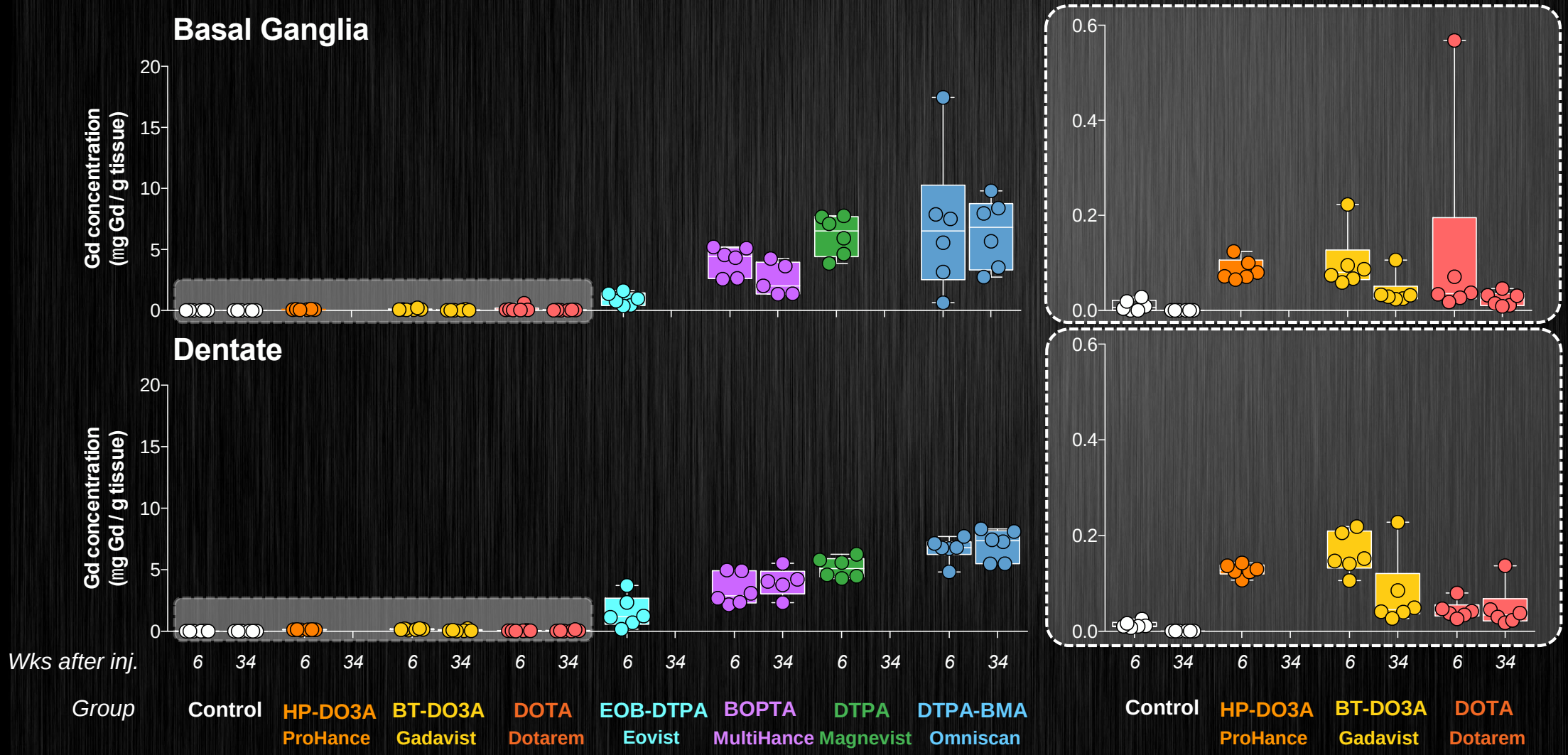


- Gadolinium tissue concentration is not entirely class-dependent
- Gadavist levels are much higher than ProHance, and within 2-4 –fold of linear agents.
- Similar pattern of differentiation is seen in other organs, at higher [Gd].

McDonald et al, in press, Radiology 2017

Macrocyclic vs. Linear GBCAs

ICP-MS RESULTS – BRAIN



Gadolinium Retention

EMA AND FDA RECOMMENDATIONS

Findings	EMA	FDA
Standard for drug suspension	Precautionary principle	Evidence of harm
Current standing	Linear GBCAs banned*	No current ban
Request for ongoing research	No	Yes
Involved in ongoing research	No	Yes

QUESTION: Is Gadolinium Toxic?

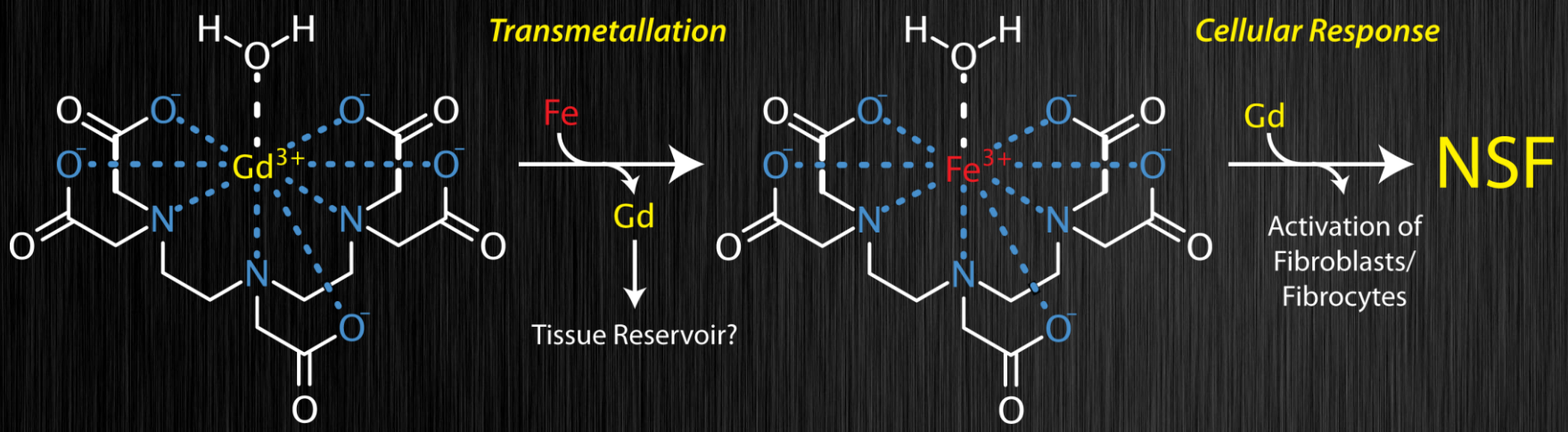
YES

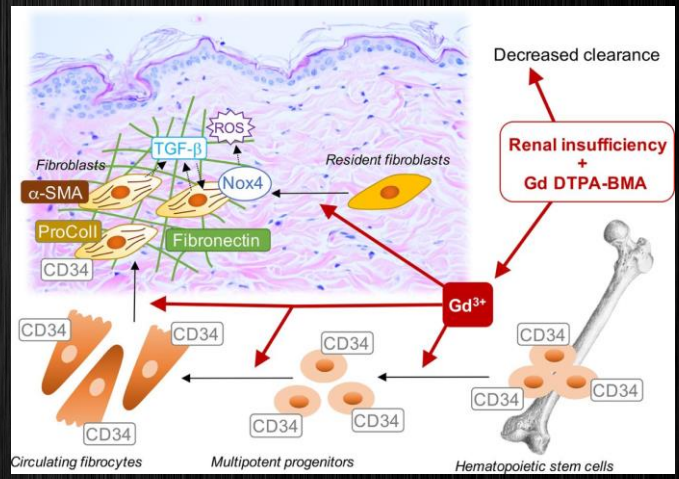
QUESTION: Are Gadolinium Deposits Toxic?

?

Are Gd Deposits Toxic?

NSF & OTHER MECHANISMS





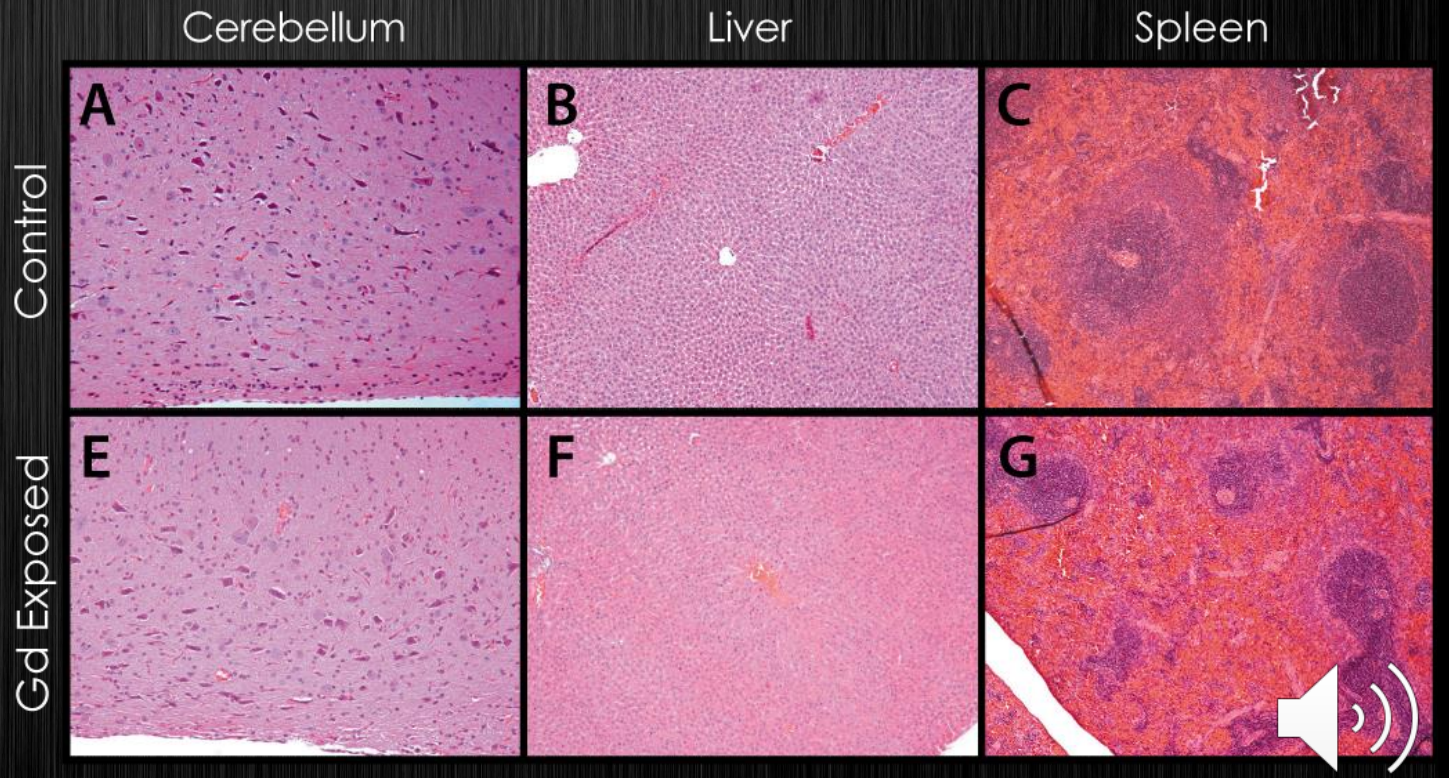
Mechanisms	Study	Species/cells	Reference
Nephrotoxicity (reduced glomerular filtration rate)	In vitro	Renal tubular cells	Heinrich et al. 2007
Nephrotoxicity (acute tubular necrosis)	In vivo	Pigs	Elmstahl et al. 2006
Hematoxicity (reduced WBC count)	Case report	Human	Akgun et al. 2006
Hepatotoxicity (vacuolar degeneration, disorganized hepatic cords)	In vivo	Mice	Chen et al 2015
Pancreatitis	Case report	Human	Blasco-Perrin et al. 2013
Neurotoxicity (myoclonus, ataxia, tremor, neuronal death, and hemorrhage)	In vivo	Rats	Ray et al. 1996
Neurotoxicity (encephalopathy)	Case report	Human	Hui and Mullins 2009

Are Gd Deposits Toxic?

HISTOLOGY RESULTS

- Multiple studies have found no histologic changes in brain tissues of patients exposed to GBCAs (*McDonald et al, 2015, McDonald et al, 2017, Fingerhut et al, 2018*).

- Numerous preclinical studies have also not found histologic changes due to GBCA administration.



McDonald et al, Radiology 2017

Are Gd Deposits Clinically Significant?

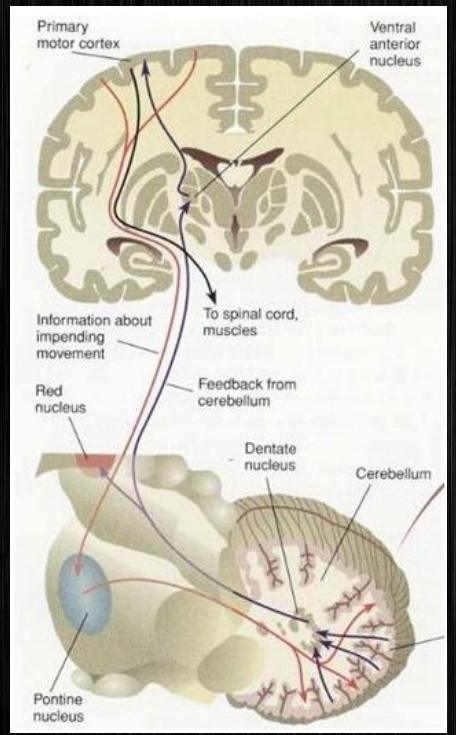
- The Single Most Important Question
- Real World Data: Over 450 million doses of IV GBCAs have been administered over the past 30 years (Linear > Macrocyclic) WITHOUT widespread reports of neurotoxicity. However, scientific proof is needed!
- How Do We Go About Testing This?
  1. Preclinical Models
  2. Retrospective Human Data
  3. Prospective Human Data

Are Gd Deposits Clinically Significant?

WHAT SYMPTOMS TO EXAMINE?

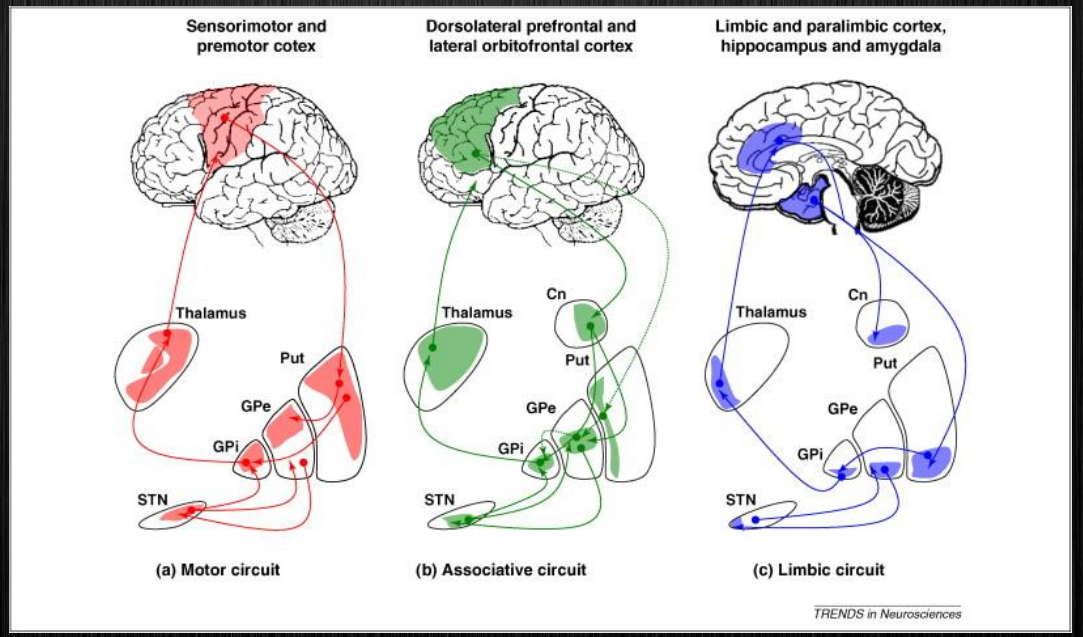
Dentate Nucleus

- Coordination (planning and initiation) of limb movement



Basal Ganglia

- learning and memory
- coordination of movement; filtering out undesired movements; posture and balance
- implicated in anxiety and mood disorders



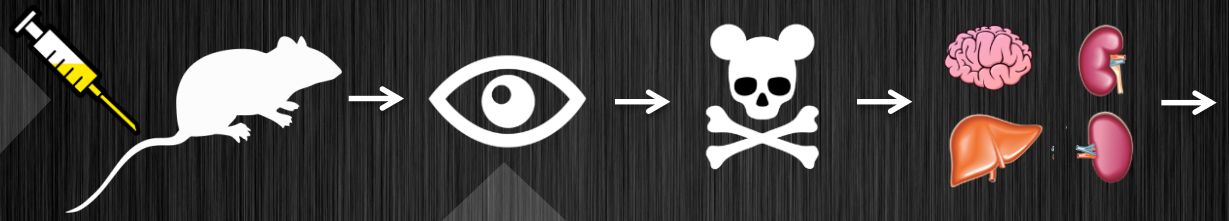
Krack, P., et al. "Trends in Neurosciences 33(10): 474-484

Are Gd Deposits Clinically Significant?

USING A PRECLINICAL RAT MODEL TO STUDY THE EFFECT OF GD ON LOCOMOTOR, COGNITIVE/MEMORY, MOOD & BALANCE/COORDINATION FUNCTION

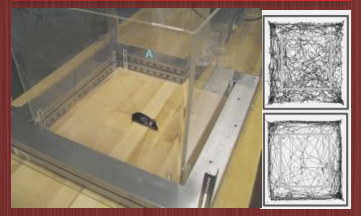
Study Groups

Group	Agent	Dose (mmol/kg)
1	Saline	-
2	Gadopentetate	2.5
3	Gadodiamide	2.5
4	Gadoversetamide	2.5
5	Gadobenate	2.5
6	Gadoteridol	2.5
7	Gadobutrol	2.5
8	Gadoterate	2.5
9	Gadoxetate	2.5
10	Gadodiamide	0.6
11	Gadoterate	0.6

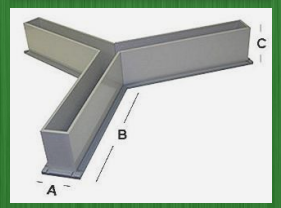


Mayo Clinic Rodent Behavioral Core Facility

Open Field Arena



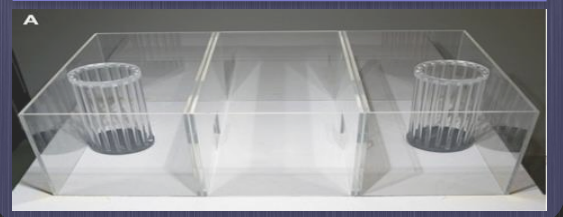
Y-maze



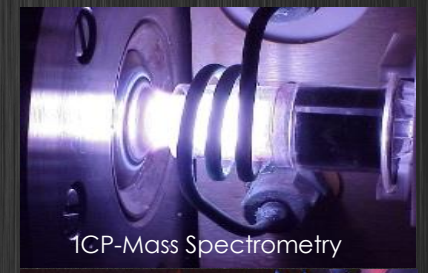
Novel Object Recognition

Ladder Rung Task

Social Anxiety Test



Tissue Analysis



1CP-Mass Spectrometry

Transmission Electron Microscopy

Light Microscopy

Are Gd Deposits Clinically Significant?

USING A PRECLINICAL RAT MODEL TO STUDY THE EFFECT OF GD ON LOCOMOTOR, COGNITIVE/MEMORY, MOOD & BALANCE/COORDINATION FUNCTION

- No differences between GBCA-exposed and control rats were observed for any behavioral test.

Are Gd Deposits Clinically Significant?

NEGATIVE FINDINGS

Findings	GBCA	Species	Condition	Reference
No increased risk of Parkinsonism diagnosis	Multiple	Human	No specific	Welk et al. 2016
No change in neurologic test results, no increased risk of developing mild cognitive impairment	Gadodiamide	Human	No specific	McDonald et al. 2016
No signs of cerebellar toxicity	Gadoterate	Human	No specific	Perrotta et al. 2017
No correlation between T1 hyperintensity and worse clinical outcomes	Multiple	Human	MS	Cocozza et al. 2019
No neurological and neurocognitive/psychological abnormalities	Gadodiamide	Human	Crohn's	Mallio et al. 2019
No association with MS severity	Gadodiamide	Human	MS	Zivadinov et al. 2019
No neurological/neuropsychological impairment in the DN and GP	Multiple	Human	GBM	Vymazal et al. 2019

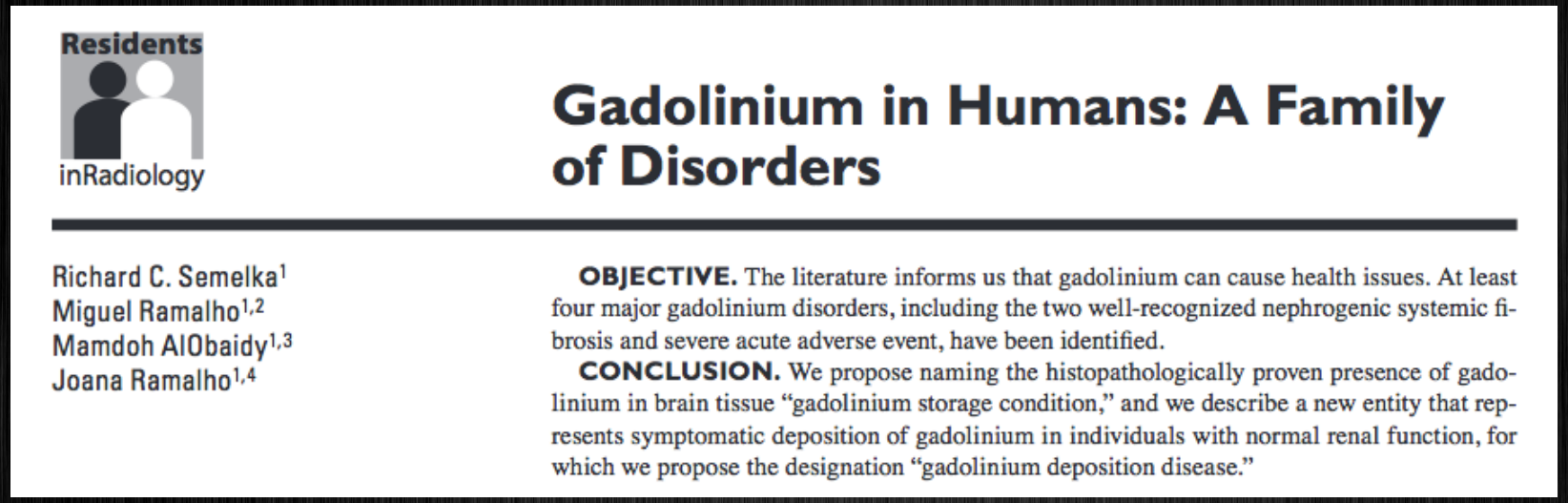
Are Gd Deposits Clinically Significant?

POTENTIALLY POSITIVE FINDINGS

Findings	GBCA	Species	Condition	Reference
Increased T1 signal in dentate nucleus in exposed patients correlated with lower verbal fluency scores	Multiple	Human	MS	Forslin et al. 2017
In utero GBCA exposure was associated with increased risk of various skin conditions, stillbirth, and neonatal death	Multiple	Human	Pregnancy	Ray et al. 2016

Are Gd Deposits Clinically Significant?

GADOLINIUM DEPOSITION DISEASE



Residents
inRadiology

Gadolinium in Humans: A Family of Disorders

Richard C. Semelka[1]
Miguel Ramalho[1,2]
Mamdoh AlObaidy[1,3]
Joana Ramalho[1,4]

OBJECTIVE. The literature informs us that gadolinium can cause health issues. At least four major gadolinium disorders, including the two well-recognized nephrogenic systemic fibrosis and severe acute adverse event, have been identified.

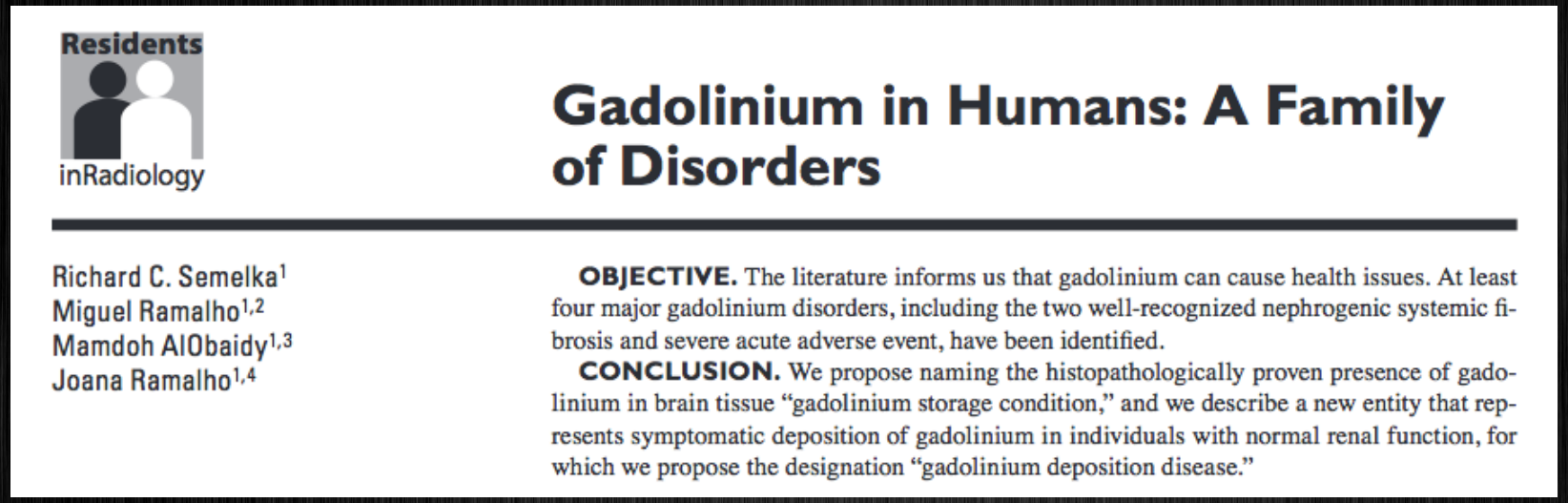
CONCLUSION. We propose naming the histopathologically proven presence of gadolinium in brain tissue "gadolinium storage condition," and we describe a new entity that represents symptomatic deposition of gadolinium in individuals with normal renal function, for which we propose the designation "gadolinium deposition disease."

- Studies encompassing 139 patients.
- Constellation of symptoms, including neuropathic pain, fatigue, joint stiffness, headache, cognition changes.

Semelka RC, et al AJR 2016;207:229-233

Are Gd Deposits Clinically Significant?

GADOLINIUM DEPOSITION DISEASE



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- No control group, no way to confirm causality.
- No correlation between reported symptoms and Gd levels.
- Lots of missing data.

Semelka RC, et al AJR 2016;207:229-233

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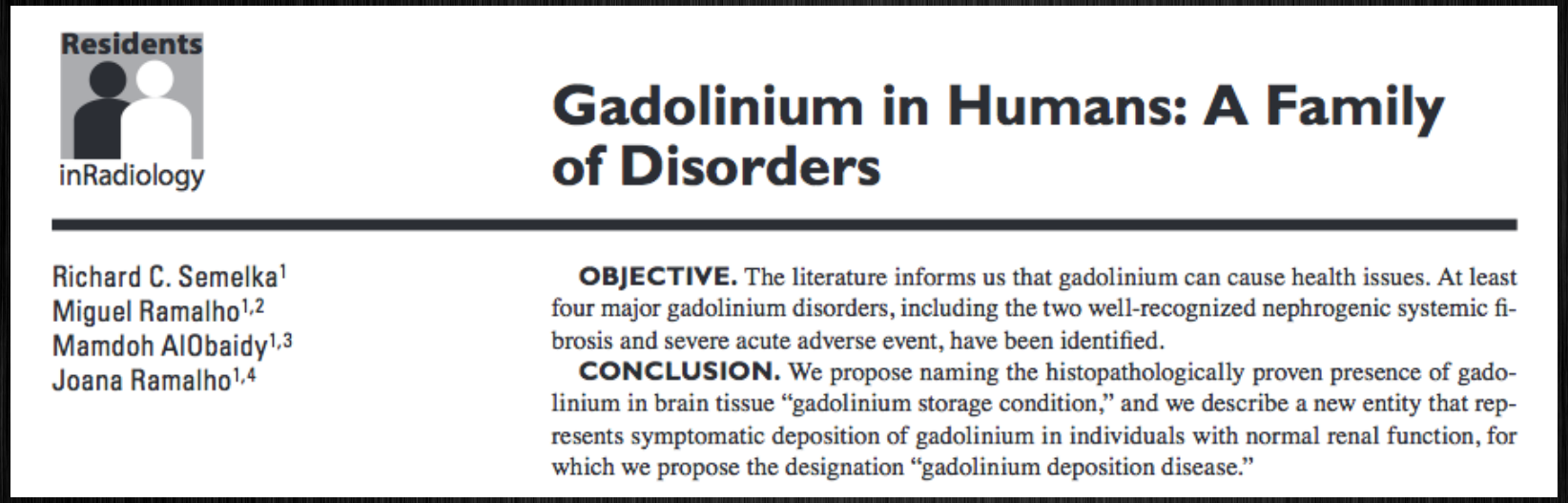
GADOLINIUM DEPOSITION DISEASE



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THE FDA DOES NOT FIND SUFFICIENT CAUSAL EVIDENCE FOR GDD

Semelka RC, et al AJR 2016;207:229-233

Are Gd Deposits Clinically Significant?

GD RETENTION LAWSUITS

Clean Sweep of Plaintiffs' Causation Experts in Gadolinium Litigation

By Michelle Yeary on August 13, 2019

POSTED IN EXPERTS

NEWS | CONTRAST MEDIA | JANUARY 17, 2020

Voluntary Dismissal of Chuck Norris Gadolinium Case Involving Bracco

The lawsuit alleging injury from the company's MR contrast agent has been closed

Should we change clinical practice?

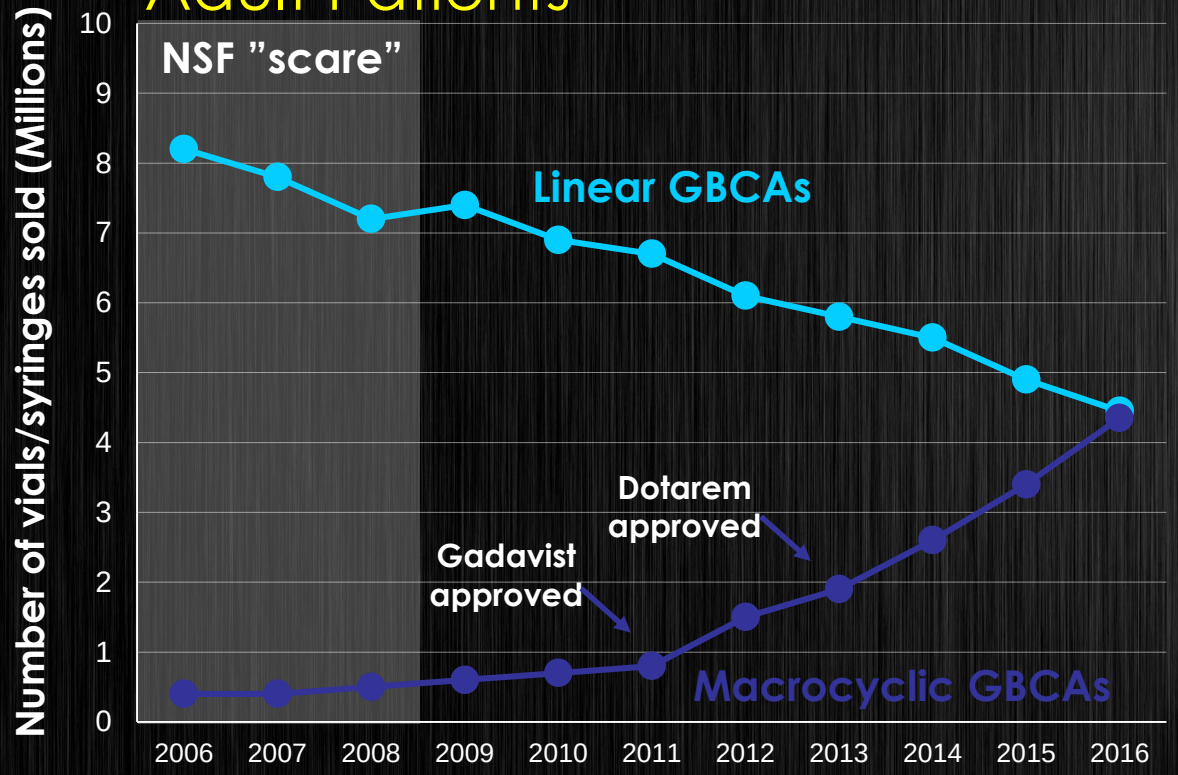
- GBCAs provide crucial, life-saving medical information.
- Weight the clinical benefit GBCAs may provide against the unknown risks of Gd retention.
- Consider multiple factors when choosing a GBCA: diagnostic efficacy, relaxivity, rate of adverse reactions, and amount of Gd deposited.

Why Not Just Use Macrocyclic GBCAs?

- No direct evidence yet that Gd retention causes harm in patients.
- However, higher amounts of Gd are retained following linear vs. macrocylic GBCAs.
- Gd has documented toxicity.
- Why not just switch to macrocylics to be safe?

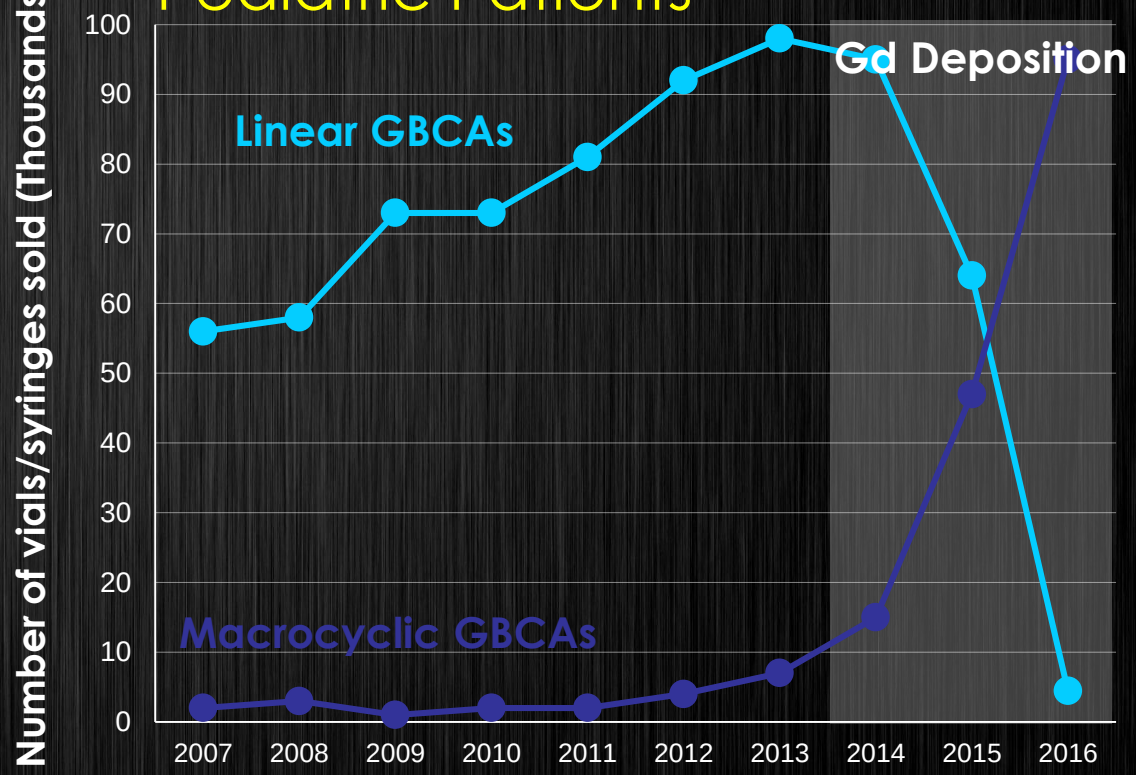
Why Not Just Use Macrocyclic GBCAs?

Adult Patients



Source: QuintilesIMS Health, IMS National Sales Perspectives. Data extracted July 2017

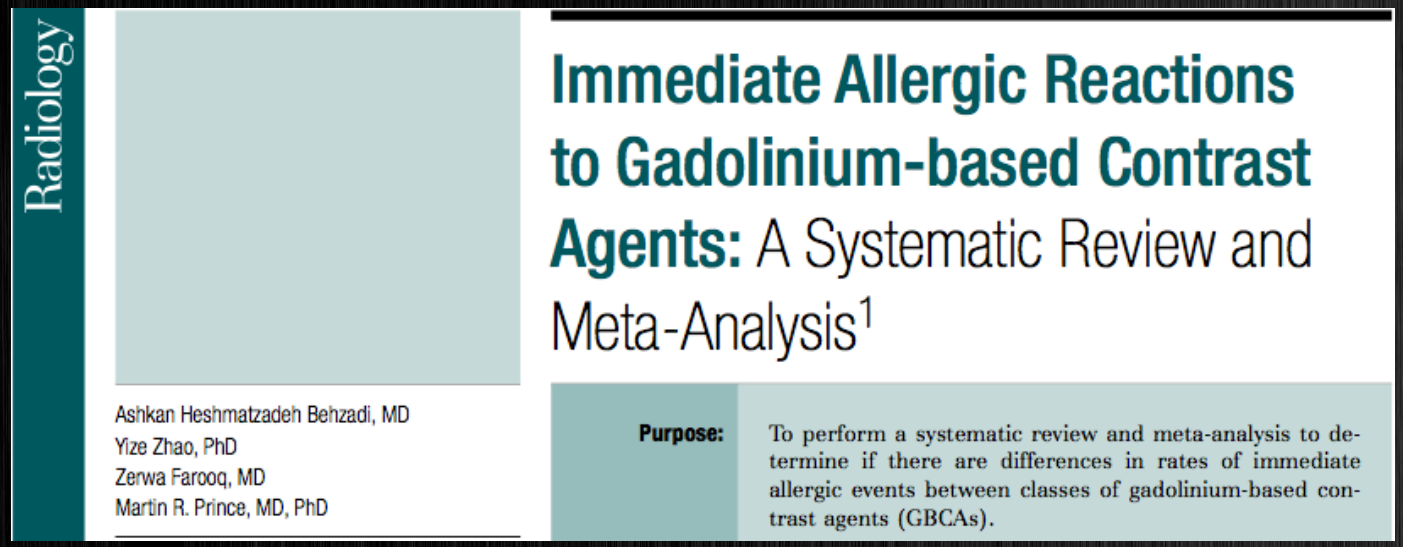
Pediatric Patients



Source: Symphony Health Solutions' PHAST Non-Retail Monthly, Data extracted Juy 2017

Why Not Just Use Macrocyclic GBCAs?

OTHER GBCA SAFETY CONSIDERATIONS

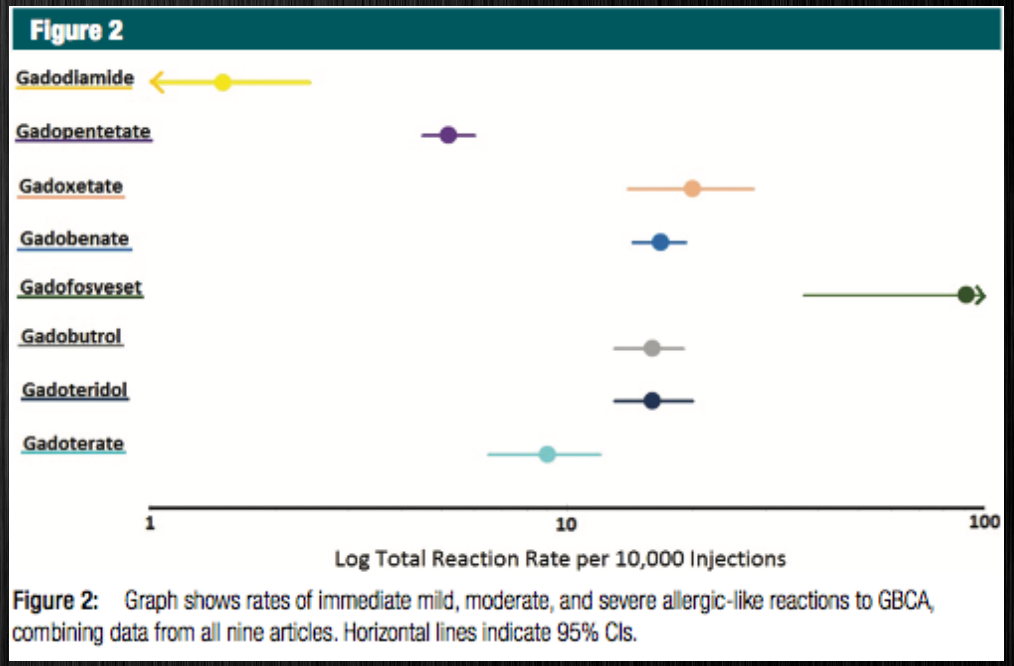


Radiology

Immediate Allergic Reactions to Gadolinium-based Contrast Agents: A Systematic Review and Meta-Analysis[1]

Ashkan Heshmatzadeh Behzadi, MD
Yize Zhao, PhD
Zerwa Farooq, MD
Martin R. Prince, MD, PhD

Purpose: To perform a systematic review and meta-analysis to determine if there are differences in rates of immediate allergic events between classes of gadolinium-based contrast agents (GBCAs).



- Meta-analysis of 716,978 GBCA administrations.
- GBCA with highest Gd retention had lowest rate of acute reactions.

Behzadi et al, Radiology 2018

Why Not Just Use Macrocyclic GBCAs?

OTHER GBCA SAFETY CONSIDERATIONS

GBCA Used	Total Injections	Mild	Moderate	Severe	Total
All reactions					
Gadodiamide	140 645	196 (14)	70 (5)	0	266 (19)
Gadobutrol	94 109	245 (26)	92 (10)	3 (0)	340 (36)
Gadobenate dimeglumine	39 138	141 (36)	56 (14)	3 (1)	200 (51)
Gadoterate meglumine	8053	9 (11)	1 (1)	0	10 (12)
Allergic-like reaction					
Gadodiamide	140 645	76 (5)	46 (3)	0	122 (9)
Gadobutrol	94 109	107 (11)	75 (8)	3 (0)	185 (20)
Gadobenate dimeglumine	39 138	77 (20)	51 (13)	3 (1)	131 (33)
Gadoterate meglumine	8053	4 (5)	0	0	4 (5)
Physiologic reaction					
Gadodiamide	140 645	120 (9)	24 (2)	0	144 (10)
Gadobutrol	94 109	138 (15)	17 (2)	0	155 (16)
Gadobenate dimeglumine	39 138	64 (16)	5 (1)	0	69 (18)
Gadoterate meglumine	8053	5 (6)	1 (1)	0	6 (7)

- Mayo Clinic data shows a similar pattern of acute reaction rates.
- Are we replacing an unknown risk with a known one?

McDonald et al, Radiology 2019

Gadolinium Retention

SUMMARY

1. All GBCAs cause Gd deposition in the brain and other organs.
   - Macrocyclic agents deposit less.
   - Deposition is not entirely class dependent.

2. There is no strong evidence of neurotoxicity or clinical effects associated with Gd retention.

3. A risk-benefit assessment should be performed when deciding to use GBCAs and choosing a particular GBCA.

Project Collaborators

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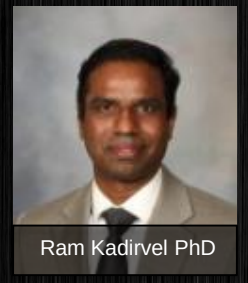
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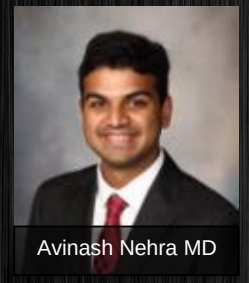
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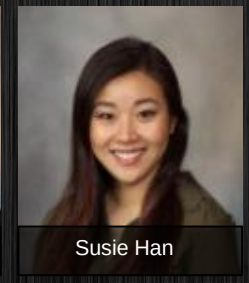
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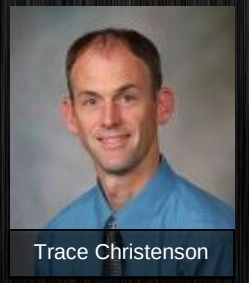
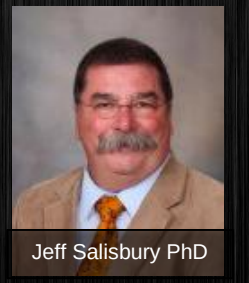

Trace Christenson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Thank you

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