How does gadolinium enter the brain?

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How Does Gadolinium Enter the Brain?

Conflicts of Interest

Active consultant for Guerbet and for Bracco; past consultant: Bayer, Bristol Meyers/Squibb, GE Healthcare, Millinckrodt/Tyco, Sanofi Winthrop.

How Does Gadolinium Enter the Brain?

The Blood-Brain and Blood CSF Barriers

1885: Paul Ehrlich (Bacteriologist)
Animal IV injection of aniline dyes stained all organs except the
brain and spinal cord.

Edwin Goldmann (protege of Ehrlich)
IV trypan blue stains the choroid plexus and meninges but not
the brain. BUT: Trypan blue injected into the CSF stains the
brain and not the rest of the body.

Stern and Gautier (1920's)
"Barrière Hématoencéphalique"
Blood Brain Barrier

Conventional and CT Metrizamide Myelography in Arnold-Chiari I Malformation and Syringomyelia

King C. Li[1]
Mario C. Chui

Four normal controls and 26 cases of Arnold-Chiari I malformations and/or syringomyelia were reviewed. The pathologic cases included five isolated Arnold-Chiari I malformations, nine communicating syringomyelia, five idiopathic syringomyelia, four posttraumatic syringomyelia, one syringomyelia with hemangioblastoma, and two postshunt syringomyelia. The objectives of this study were to compare the accuracy of conventional metrizamide myelography with CT metrizamide myelography and to study indirectly the hydrodynamics of CSF flow in syringomyelia by comparing the sequential enhancement patterns of the spinal cords and cord cavities in the different groups of patients. Twenty-five patients underwent conventional metrizamide myelography immediately before CT metrizamide myelography, and one patient underwent CT metrizamide myelography only. Scans were obtained 1–2 hr, 4–8 hr, and 12–24 hr after injection of metrizamide, but not all patients were scanned during all three intervals. CT metrizamide myelography was found to be more sensitive than conventional metrizamide myelography in the diagnosis of both Arnold-Chiari I malformation and syringomyelia. Performing just an immediate and a delayed scan was found to be more cost-effective than doing all three scans. Contrary to previous reports, it was found that delayed (12–24 hr) scans demonstrated more syrinx cavities than intermediate ones. In studying the sequential enhancement patterns of the spinal cords and cord cavities, some interesting trends were observed that tend to support the theories of Aboulker and of Ball and Dayan of transneural passage of CSF into cord cavities in syringomyelia.

Almost a century ago, Chiari described two kinds of caudal ectopia of the hindbrain [1, 2]. In this study, we examined only the Arnold-Chiari I malformation, which involves caudal displacement of the cerebellar tonsils [1, 3].

Syringomyelia, first coined by C. P. Ollivier in 1827, derives from two Greek words meaning "a cavity" and "the spinal marrow" [4]. Syringomyelia has been divided into five groups [5, 6]: (1) communicating syringomyelia or syringomyelia associated with developmental anomalies at the foramen magnum and posterior fossa or acquired abnormalities such as basal arachnoiditis; (2) posttraumatic syringomyelia; (3) syringomyelia as a sequela of arachnoiditis confined to the spinal canal; (4) syringomyelia associated with spinal cord tumors; and (5) idiopathic syringomyelia unrelated to any of the above categories.

Numerous theories have been proposed by different authors to explain the pathogenesis of syringomyelia, but none of these is universally accepted. The Gardner theory [7] hypothesized that impaired outflow of CSF from the fourth ventricle, caused by failure of the foramina to open between the sixth and eighth weeks of embryonic life, leads to the transmission of arterial pulsations of CSF to the central canal, thereby creating a syrinx cavity. Hence, in the "communicating" syringomyelia (of Gardner) there is a communication between the syrinx and the fourth ventricle via an open obex. However, the pathophysiologic mechanism suggested by Gardner has been the subject of a prolonged and as yet unresolved controversy, and this has led to the idea of "noncommunicating" syringomyelia. This variety usually develops as a late sequela of spinal cord trauma, arachnoiditis,
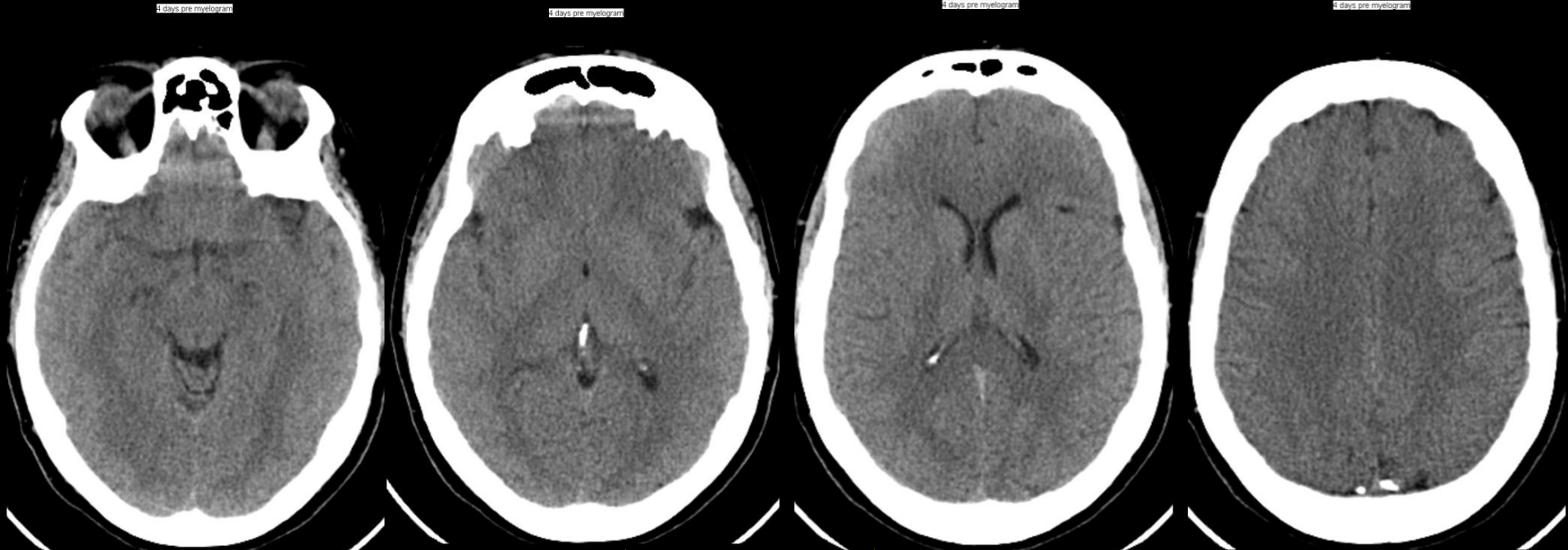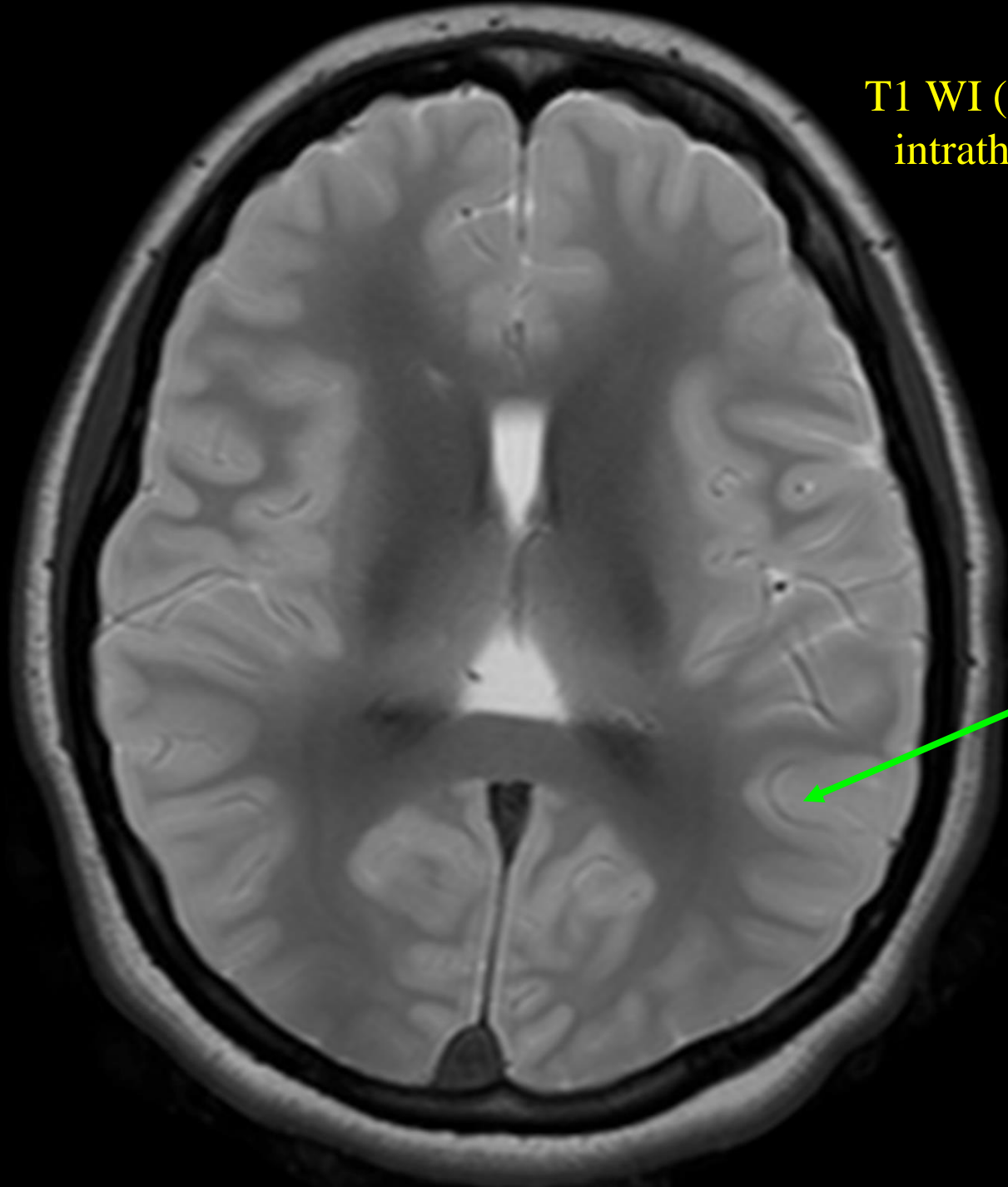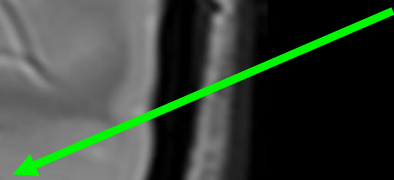
4 days pre-myelogram

(Same window
and level)
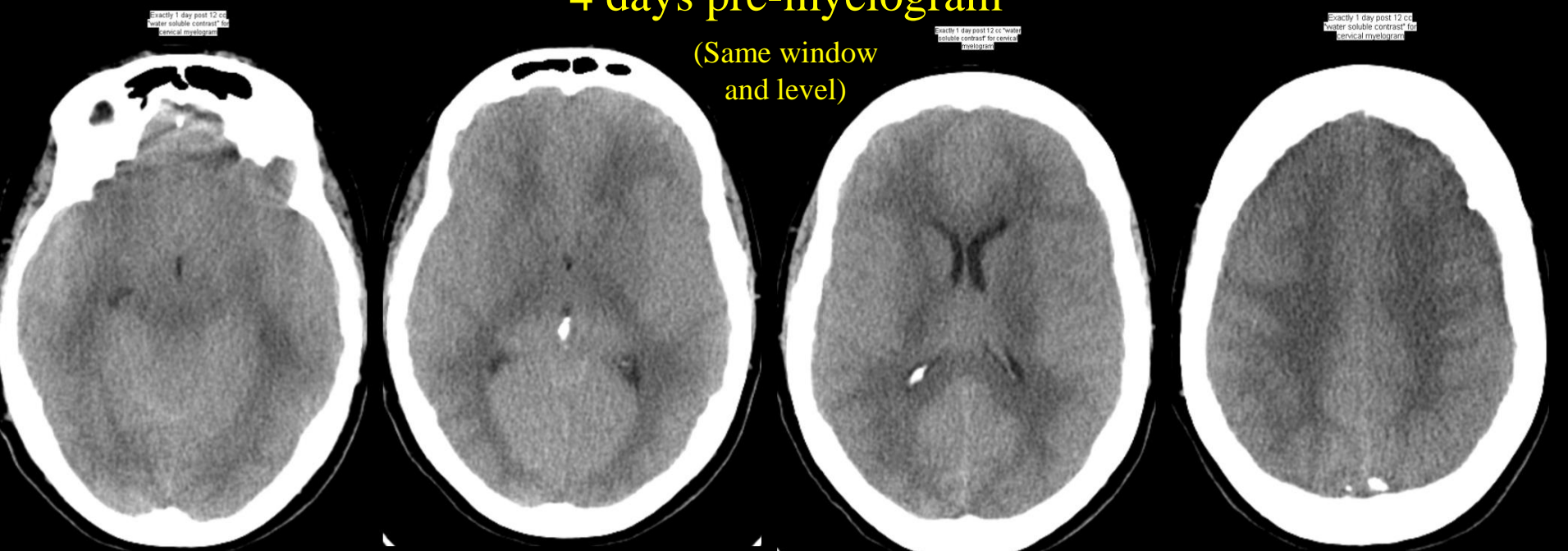
Exactly 1 day post 12 cc of water soluble contrast for cervical myelogram

T1 WI (!) 25 hours post intrathecal Prohance

Note: SI of GM >> WM

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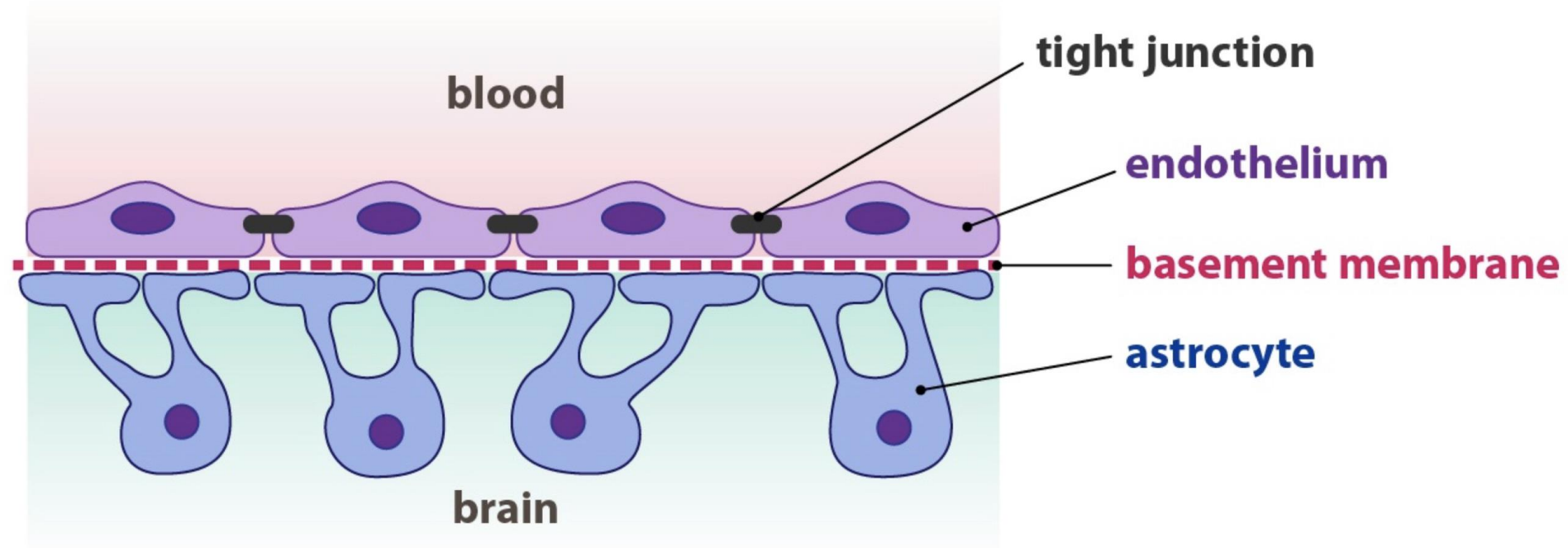
The Blood-Brain and Blood CSF Barriers

The blood brain barrier
actually consists of two barriers:

The Vascular Blood Brain Barrier
(vBBB)
The Blood-CSF-Barrier (BCB)

(There is also a Blood-Ocular Barrier…)

Vascular Blood Brain Barrier

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Mechanisms of the Vascular Blood Brain Barrier

The Vascular BBB is thought of as essentially being a "neuromuscular unit":
- A) Tight junctions
- B) Enzymatic reactions
- C) Neurotransmitter signaling
- D) Passive diffusion
- E) Facilitated diffusion
- F) Active transport

How Does Gadolinium Enter the Brain?

Anatomy of the Blood CSF Barrier

A) Total surface area ~$2m^2$ - $5m^2$
B) LOCATION:
   i)   Choroid plexus
   ii) Median eminence
   iii) Pituitary gland
   iv) Subfornical organ
   v)   Lamina terminalis
   vi) Area postrema

Blood CSF Barrier
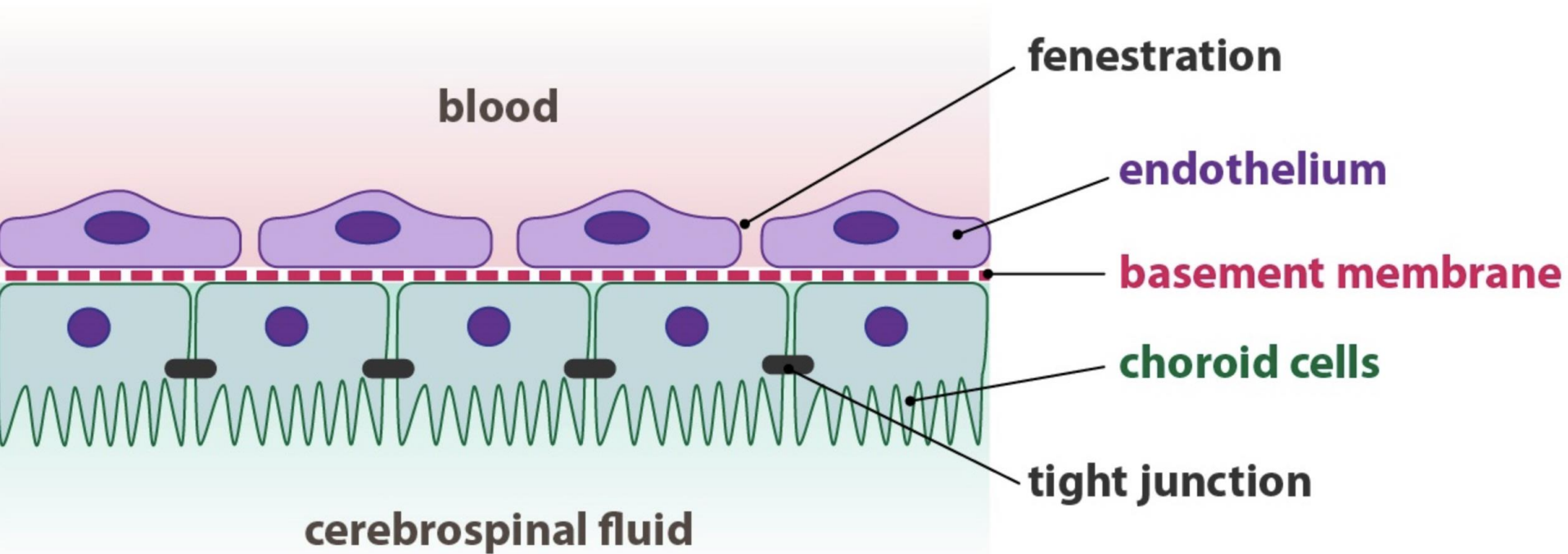
How Does Gadolinium Enter the Brain?

Cerebrospinal Fluid (CSF)

A) ~150 ml of CSF (125 in brain/spinal subarachnoid spaces plus 25 in the ventricles)

B) 500 ml generated/created/24 hours

C) Choroid plexus

   i) CONTROVERSY: Most seem to say that CSF is made by choroid plexus and ONLY choroid plexus; some say that up to 25-40% of CSF is generated/created by brain interstitial fluid, ependyma, and capillaries

How Does Gadolinium Enter the Brain?

Cerebrospinal Fluid (CSF)

    D) CSF resorption
        i) Cranial and spinal arachnoid granulations/arachnoid villi
            a) Finger-like endothelium-lined protrusions of the arachnoid outer layer through the dura mater into the venous sinus lumen
            b) Spinal arachnoid granulations are associated with the epidural venous plexus
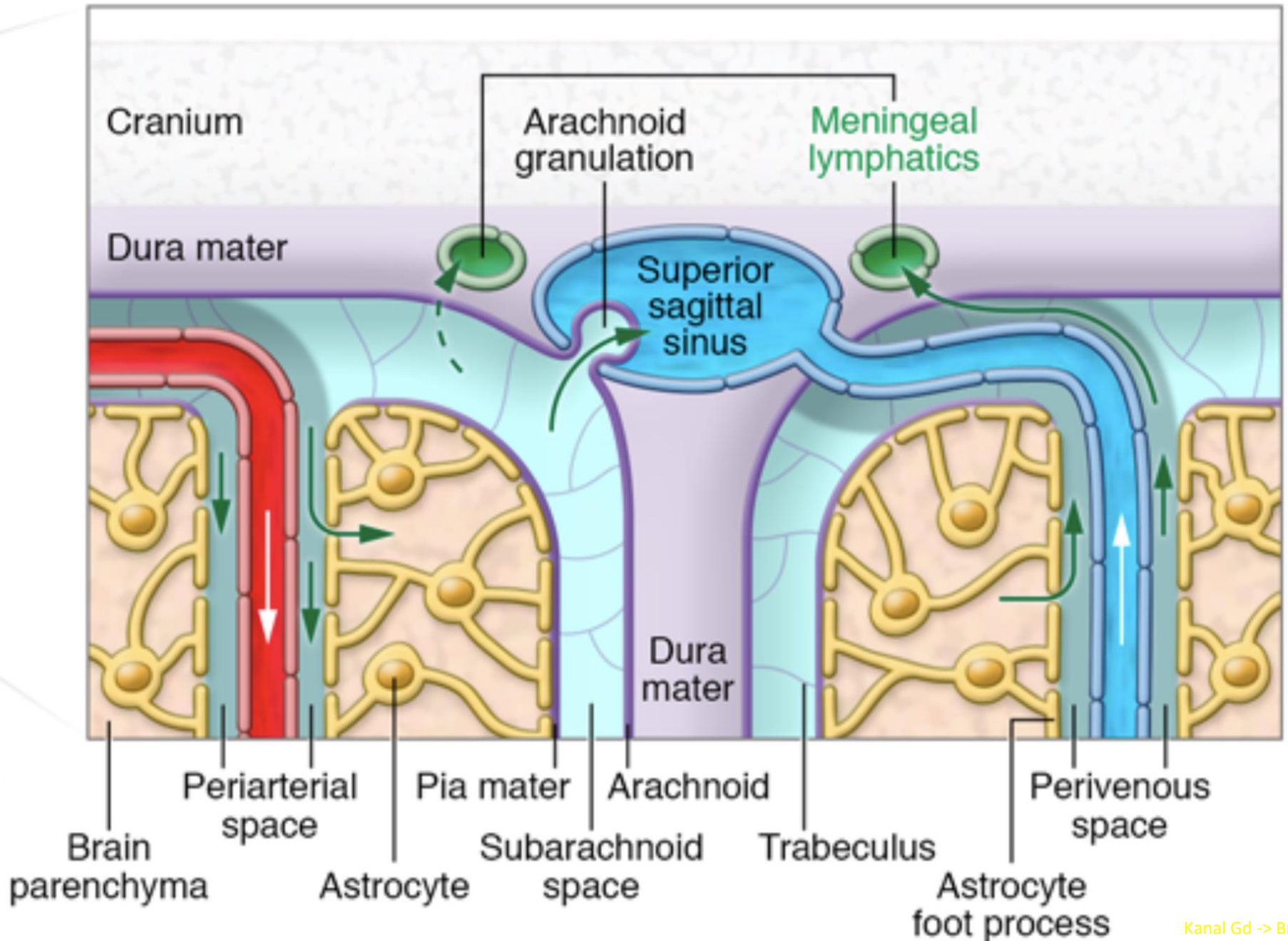   ii) Cranial and spinal nerve sheaths
        iii) Cribriform plate
        iv) Adventitia of cerebral arteries into the lymphatic system

Glymphatic System

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Sami H. Erbay
Rafeeque A. Bhadelia

Gadolinium enhancement of cerebrospinal fluid in a patient with renal failure

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Abstract Gadolinium based MRI contrast agents are considered very safe due to their well known pharmacologic properties and elimination mechanisms. In this paper, we present a unique case in whom transient enhancement of CSF with contrast is seen. Severe renal failure is demonstrated to be responsible for this finding. The diagnostic criteria for everyday clinical setting and possible clinical implications are discussed.

Keywords Gadolinium · Contrast agents · Cerebrospinal fluid

Introduction

Transient gadolinium enhancement of cerebrospinal fluid (CSF) on fluid attenuation inversion recovery (FLAIR) images can be seen in subjects without significant meningeal disease [1]. However, detection of CSF enhancement on conventional T1-weighted images usually implies extensive meningeal or superficial brain disease [2–4]. To our knowledge, such a phenomenon has not been reported in the absence of a meningeal disease process. We present a case of CSF enhancement by gadolinium on T1-weighted and FLAIR images which we believe was due to a combination of a high dose of gadolinium and renal failure.

Case report

This 70-year-old female patient with multiple medical problems including CREST syndrome, chronic renal failure, hypertension, and coronary artery disease had ongoing *Clostridium difficile* diarrhea for almost 8 months, with worsening renal failure (creatinine levels being elevated to 2.7 from the baseline value of 1.9 mg/dl). Although the renal sonogram showed small and echogenic kidneys, her complicated medical course and slow recovery raised a suspicion of underlying renovascular disease, prompting magnetic resonance angiography (MRA) of the renal arteries at an outside institution. Renal MRA performed following an injection of 0.2 mmol/kg of Gadoteridol revealed no significant abnormality. The patient presented to our institution the following day with declining mental status without any focal neurological findings. At the same time she had also developed severe pancolitis with toxic megacolon. MRI of the brain revealed that both the ventricular and subarachnoid CSF had diffusely increased signals on FLAIR images (Fig. 1 a). The T1-weighted images demonstrated increased signal of the subarachnoid CSF (Fig. 1 b). Additionally, there was enhancement in the nasal and nasopharyngeal mucosa, superior sagittal sinus, small vessel related infarcts and perivascular spaces (Fig. 1 a, c). Lumbar puncture done on the same day revealed clear–colorless CSF, normal cytology, normal cell count (two white and three red blood cells), glucose of 64 mg/dl (serum glucose same day 98 mg/dl), protein 60 mg/dl (normal range in our laboratory being 15–45 mg/dl). After excluding the possibilities of meningitis, subarachnoid hemorrhage or meningeal carcinomatosis by laboratory analysis of CSF we performed MR imaging of the CSF

creatinine 2.7
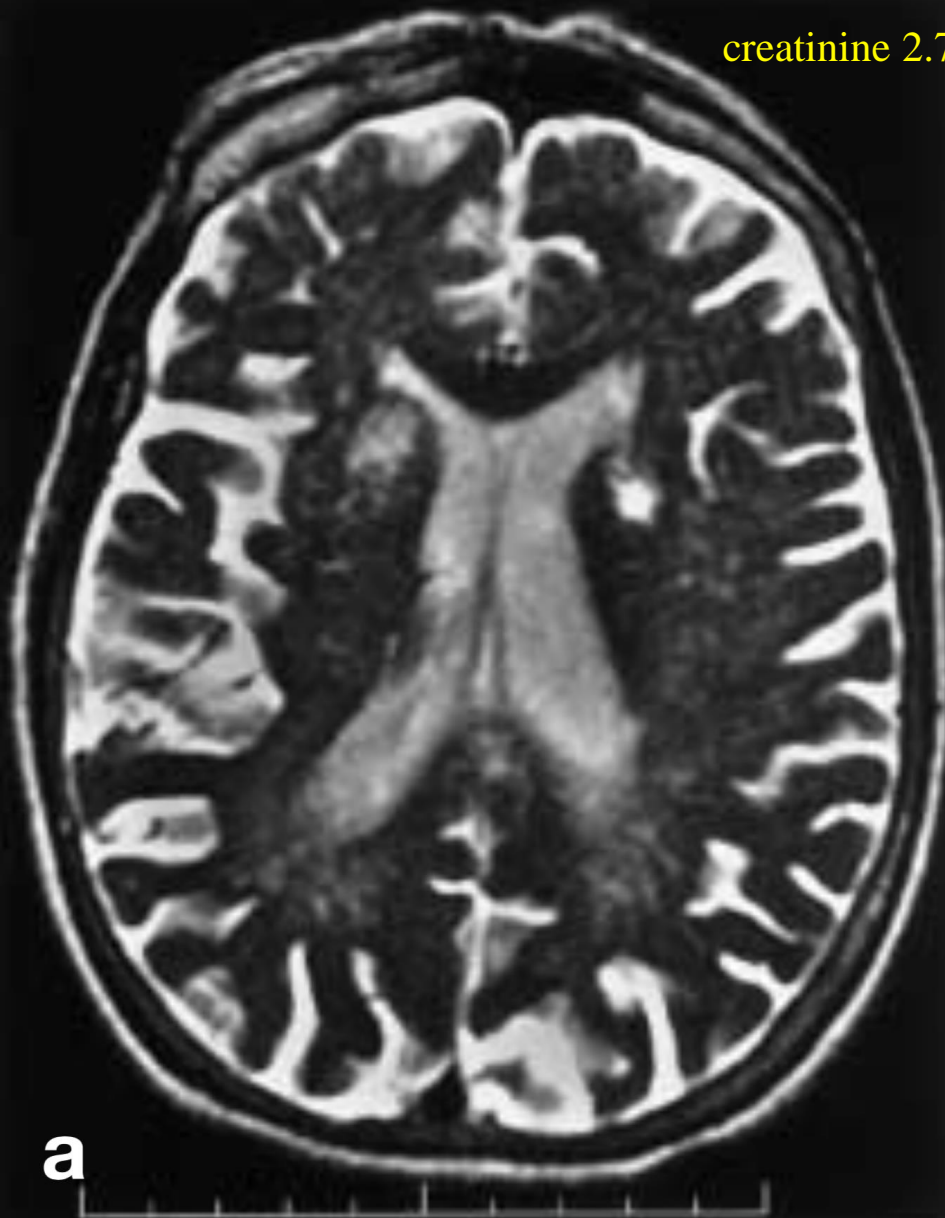
post dialysis

FLAIR 9002/154/2200
1 day post iv
double dose gadoteridol
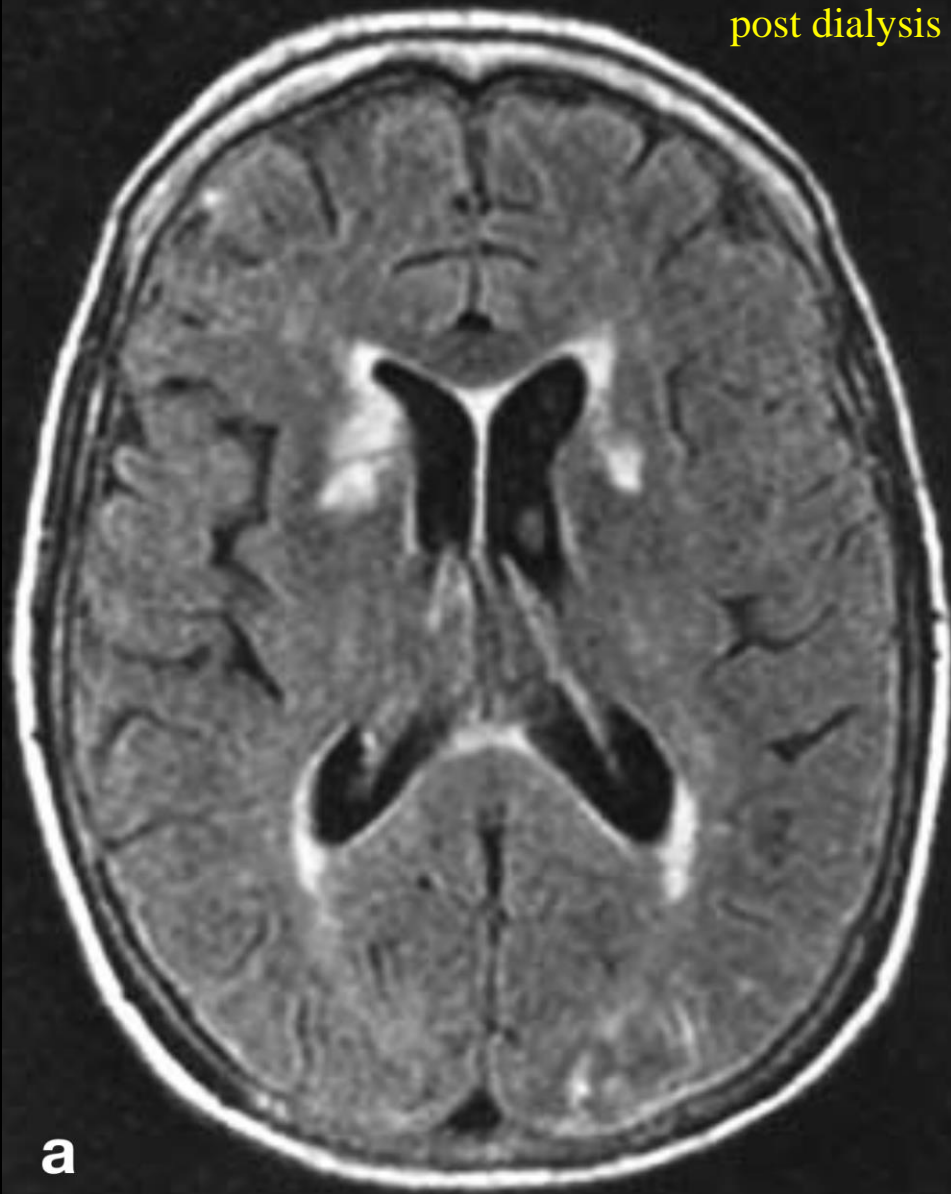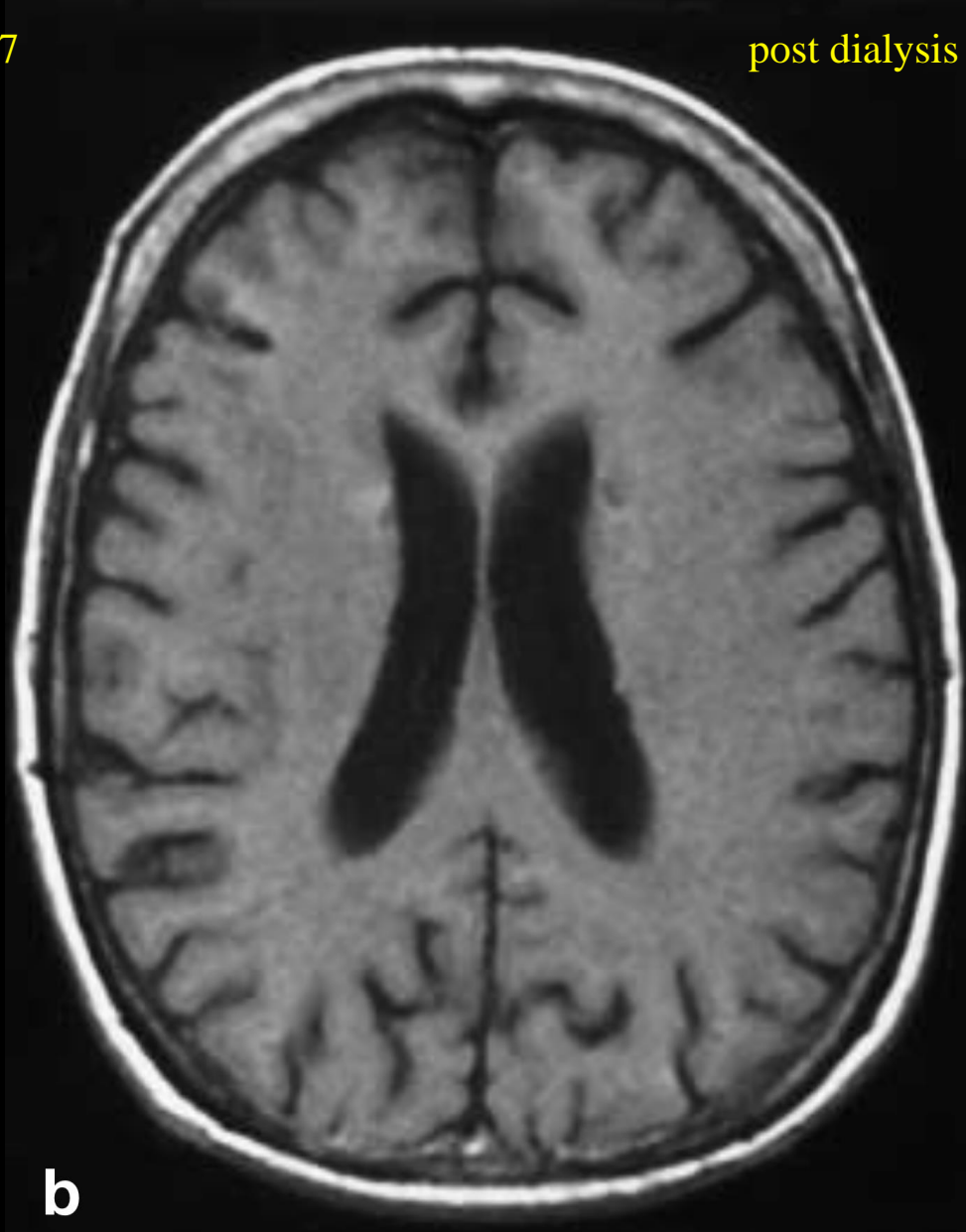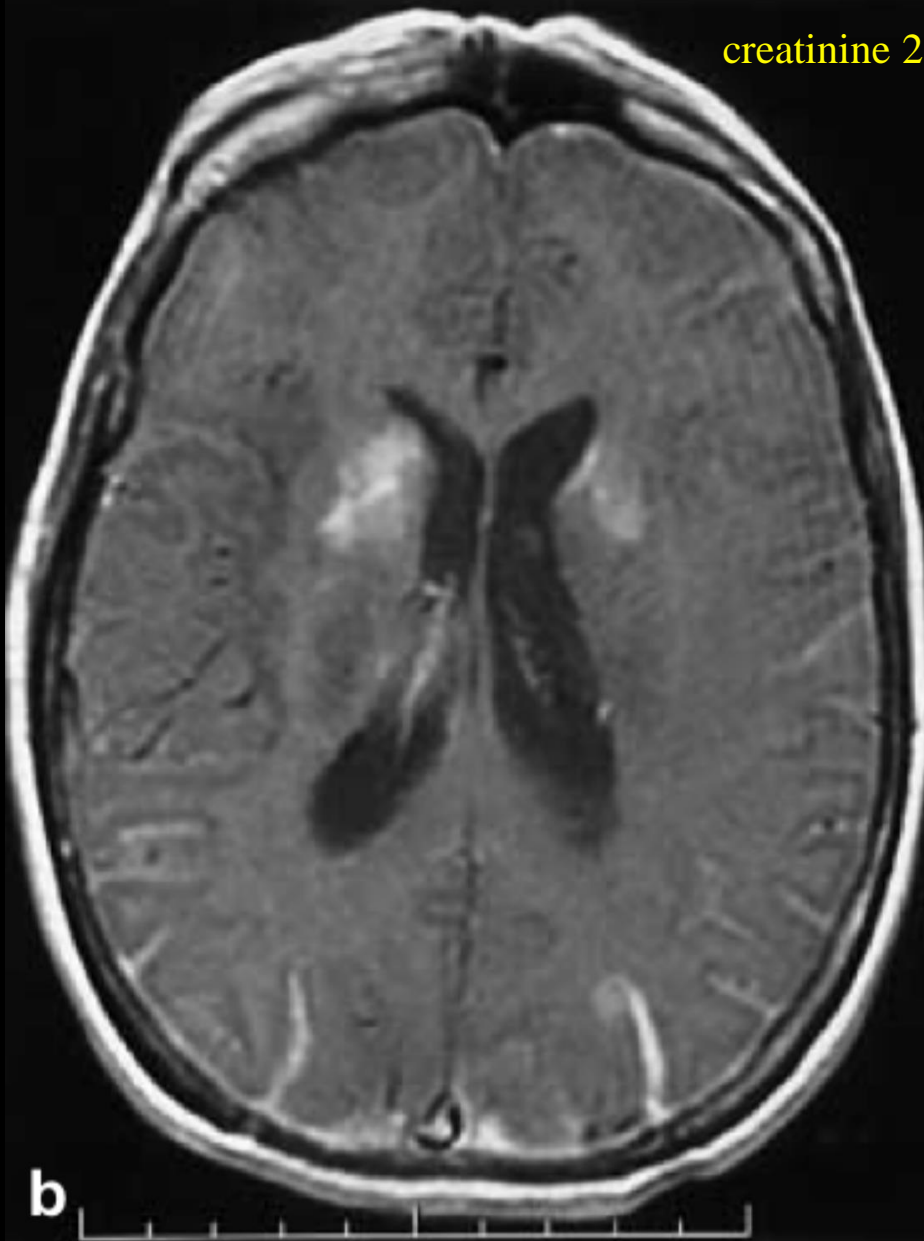
FLAIR 9002/154/2200
f/u ~2 day post iv
double dose gadoteridol Kanal Gd -> Brain?

creatinine 2.7

post dialysis

TR/TE = 550/16
1 day post iv
double dose gadoteridol

TR/TE = 500/16
f/u ~2 day post iv
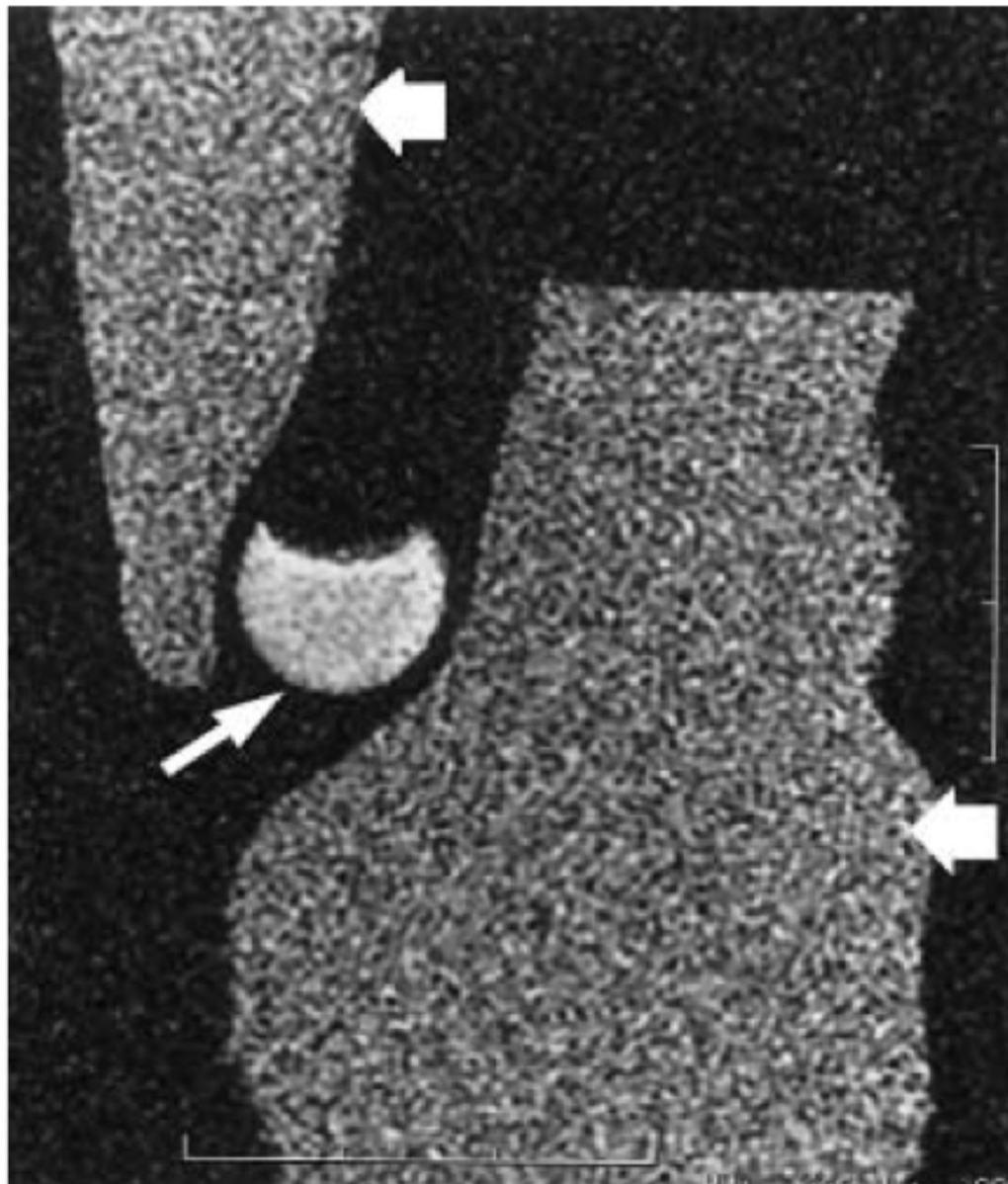double dose gadoteridol Kanal Gd -> Brain?

Fig. 2 Axial T1-weighted image of the CSF sample shows a bright signal in the test tube (*arrow*) compared with the low back-signal of normal saline solutions (*small thick arrows*)

1.5 PMR4OW
Ex:18319
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ax T2 flair
Offset:14.2435
Cont:

M; 069Y;

4/2/2005 9:31:16

2 days
post-contrast

R

FL:90.0
TR: 9002
TE: 165.532
TI: 2200

NEX: 1
ET: 0
FOV 220.0 mm/100%
5.00 mm thk/6.00 sp
Matrix 256 x 192
FC_SLICE_AX_GEMS/FC/VB_GEMS/EDR_GEMS/FILTERED_GEMS

Operator: GSS
w/l 354/278

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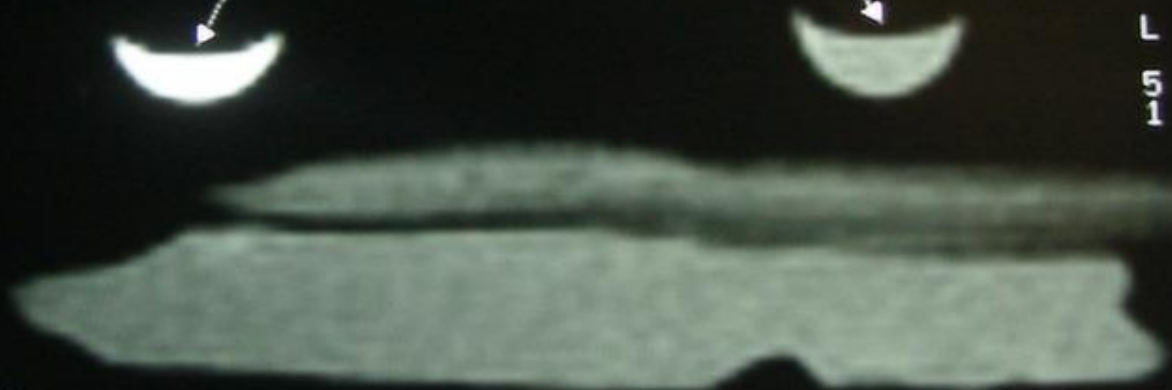
Immediately pre-Gd: 3/22/06 1812 hours
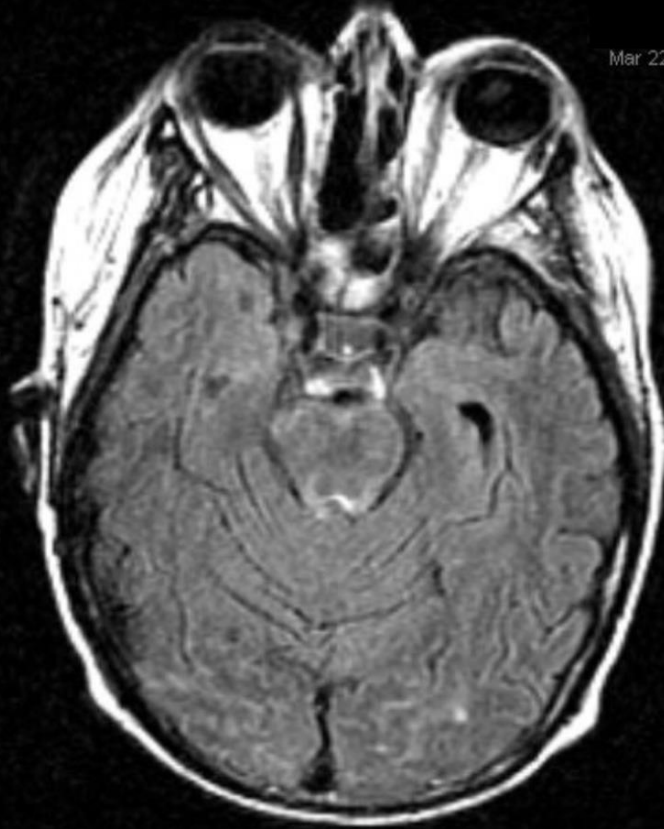
1 day post-Gd: 3/23/06 1953 hours
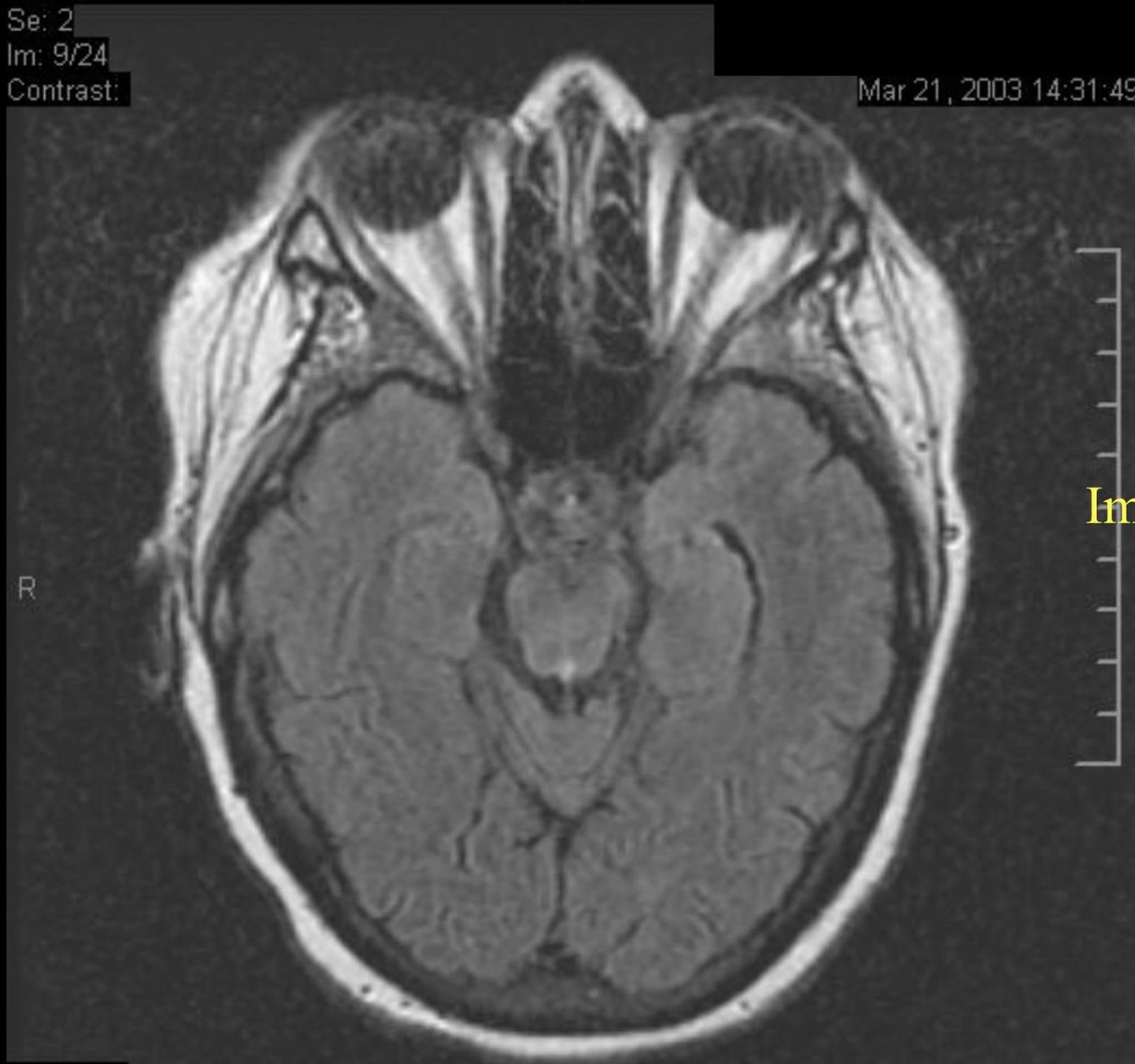
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Immediately
pre-Gd

15000.000000 PMR2OCO
7574358

A

UPMC Health Svs Presbv

Se: 6
Im: 12/24
Contrast:

Mar 25, 2003 19:24:17

R
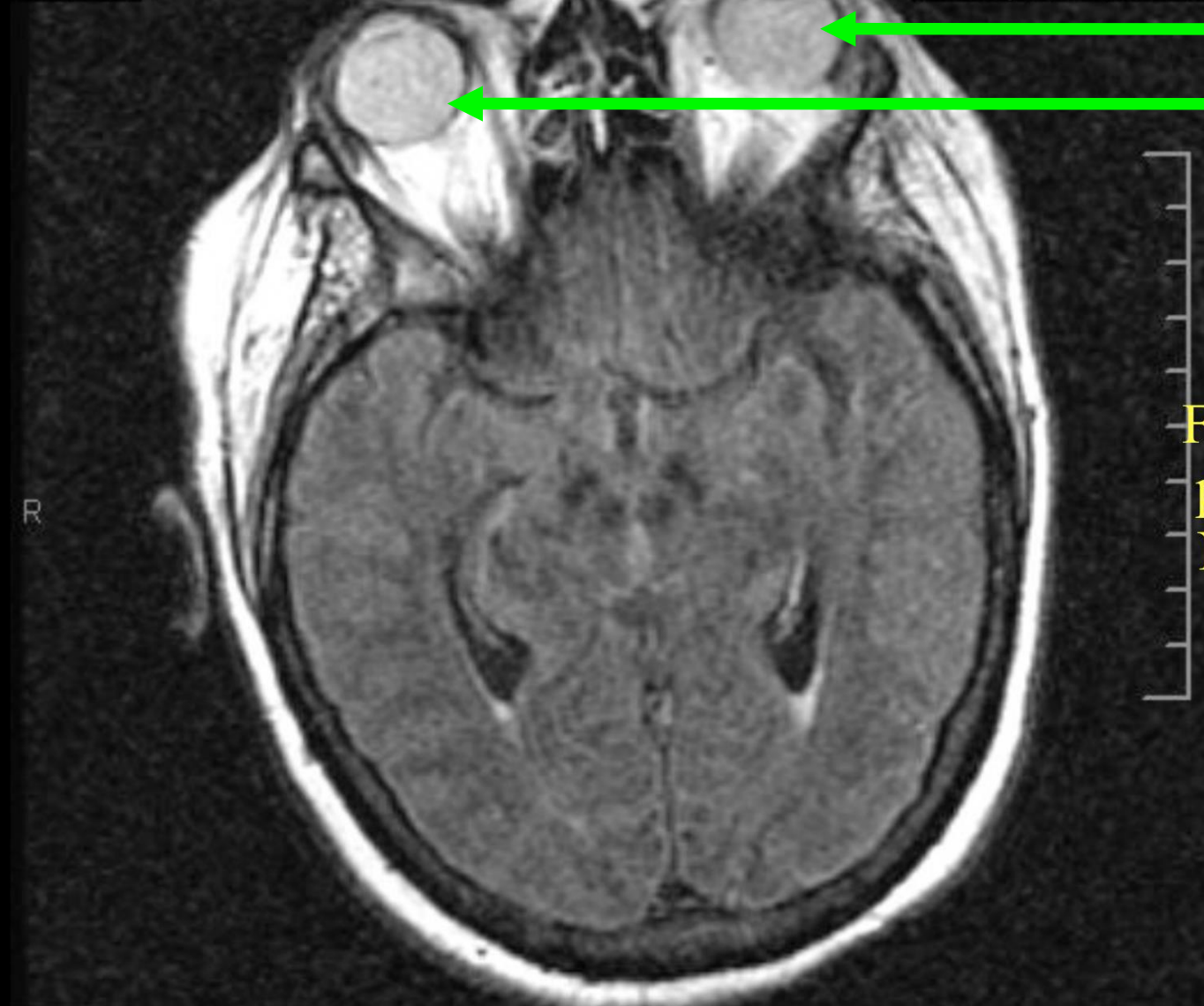
Four days
post-Gd;
Note the
orbits

ax T2 flair
5.00 mm thk/6 sp

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Penetration and distribution of gadolinium-based contrast agents into the cerebrospinal fluid in healthy rats: a potential pathway

Methods GBCA infiltration and distribution in the CSF were investigated in healthy rats using repeated fluid-attenuated MRI up to 4 h after high-dose (1.8 mmol/kg) administration of six marketed and one experimental GBCA. Additionally, gadolinium measurements in CSF, blood and brain tissue samples (after 24 h) were performed using inductively coupled plasma mass spectrometry.

Conclusions In contrast to the brain signal hyperintensities, no differences in penetration and distribution into the CSF of healthy rats exist among the marketed GBCAs.

sclerosis or neoplastic diseases [4–12]. A correlation between these signal hyperintensities in the dentate nucleus (DN) and globus pallidus (GP) and the number of contrast-enhanced MRI examinations was first described by Kanda et al. in 2014 [4]. Subsequent autopsy studies verified the presence of gadolinium in enhanced brain structures and suggest a

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Kanal Gd -> Brain?

cerebellum and pons were also taken. The following GBCAs were investigated: gadopentetate dimeglumine (Magnevist, Bayer Vital GmbH, Leverkusen, Germany), gadodiamide (Omniscan, GE Healthcare Buchler GmbH, Braunschweig, Germany), gadobenate dimeglumine (MultiHance, Bracco Imaging Deutschland GmbH, Konstanz, Germany), gadobutrol (Gadovist, Bayer Vital GmbH), gadoterate meglumine (Dotarem, Guerbet GmbH, Sulzbach/Taunus, Germany) and gadoteridol (ProHance, Bracco Imaging Deutschland GmbH).

within the intravascular compartment [33]. All agents were applied intravenously at a dose of 1.8 mmol Gd/kg body weight. This dose approximates three times the human standard dose based upon body surface area normalization between rats and humans [34]. Saline administered at identical
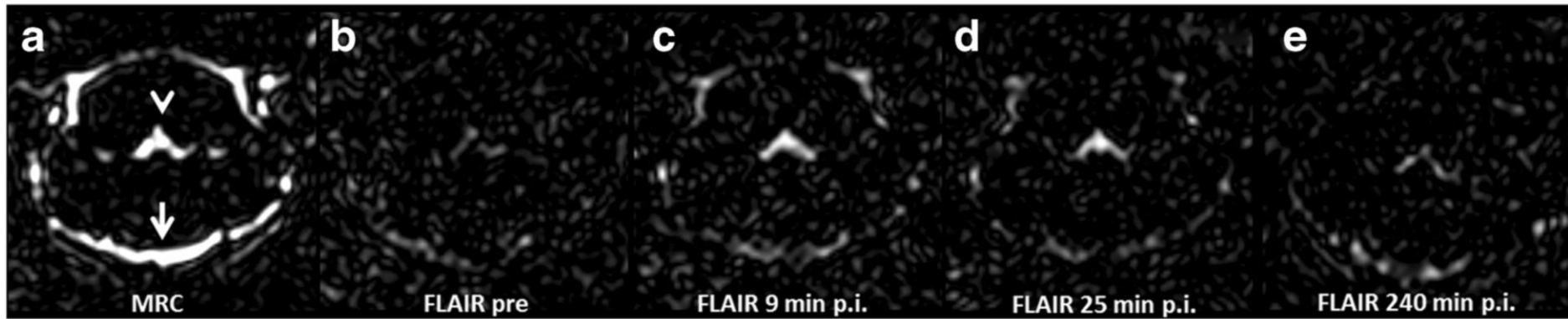
Fig. 3 Representative images. The CSF spaces were visualised by MR-cisternography (MRC), for example the fourth ventricle (arrowhead) and the subarachnoid space (arrow) (**a**). In the fluid-attenuated (FLAIR) images before GBCA injection the respective CSF signal is almost completely attenuated (**b**). After GBCA administration a clear signal enhancement of the CSF spaces was found in the FLAIR images up to 240 min post injection (p.i.) (**c–e**)

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a

3rd ventricle

gadodiamide, gadopentetate, gadobenate, gadoterate, gadobutrol, saline

aqueduct

gadodiamide, gadopentetate, gadobenate, gadoterate, gadobutrol, saline

4th ventricle

gadodiamide, gadopentetate, gadobenate, gadoterate, gadobutrol, saline

spinal subarachnoid space

gadodiamide, gadopentetate, gadobenate, gadoterate, gadobutrol, saline

lateral subarachnoid space

gadodiamide, gadopentetate, gadobenate, gadoterate, gadobutrol, saline

cerebral subarachnoid space

gadodiamide, gadopentetate, gadobenate, gadoterate, gadobutrol, saline

b

3rd ventricle

gadoteridol, gadobutrol, gadomer

aqueduct

gadoteridol, gadobutrol, gadomer

4th ventricle

gadoteridol, gadobutrol, gadomer

spinal subarachnoid space

gadoteridol, gadobutrol, gadomer

lateral subarachnoid space

gadoteridol, gadobutrol, gadomer

cerebral subarachnoid space

gadoteridol, gadobutrol, gadomer

For the marketed GBCAs, the averaged CSF gadolinium concentrations are about a factor of 7.4 higher than the respective blood concentrations at 4.5 h p.i. However, after 24 h GBCAs are almost completely cleared from the CSF, and the respective gadolinium concentrations are much lower than those in the blood. This is in contrast to gadolinium concentrations in the cerebellum and pons that are higher than those in the CSF and blood at 24 h p.i. This demonstrates that all GBCAs can be found in the brains of rats 24 h after the administration. Slight quantitative differences between the

MAJOR PAPER

Gd-based Contrast Enhancement of the Perivascular Spaces in the Basal Ganglia

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Purpose: In textbooks, the perivascular space (PVS) is described as non-enhancing after the intravenous administration of gadolinium-based contrast agent (IV-GBCA). We noticed that the PVS sometimes has high signal intensity (SI) on heavily T_2-weighted 3D-FLAIR (hT_2-FL) images obtained 4 h after IV-GBCA. The purpose of this study was to retrospectively evaluate the contrast enhancement of the PVS.

Materials and Methods: In 8 healthy subjects and 19 patients with suspected endolymphatic hydrops, magnetic resonance cisternography (MRC) and hT_2-FL images were obtained before and 4 h after a single dose of IV-GBCA. No subjects had renal insufficiency. On axial MRC at the level

Conclusion: The enhancement of the PVS at 4 h after IV-GBCA was confirmed even in subjects without renal insufficiency. It is possible that the GBCA in the blood vessels might have permeated into the cerebrospinal fluid (CSF) space and the PVS. This might be a first step in the imaging evaluation of the glymphatic system (waste clearance system) of the brain.

Keywords: *magnetic resonance imaging, perivascular space, gadolinium, glymphatic system*

Introduction

In textbooks, the perivascular space (PVS) is described as non-enhancing after the intravenous administration of gadolinium-based contrast agent (IV-GBCA).[1] The PVS exists throughout the brain, but is most frequently seen in the inferior third of the basal ganglia near the anterior commissure (AC).[1] We routinely performed magnetic resonance (MR) imaging for the assessment of endolymphatic hydrops 4 h after a single dose of IV-GBCA.[2–7]

We noticed occasionally that the PVS would have high signal intensity (SI) on heavily T_2-weighted 3D-FLAIR (hT_2-FL) images obtained 4 h after a single dose of IV-GBCA. hT_2-FL imaging has been utilized as a sensitive technique to detect very low concentrations of GBCA in fluid.[4,8,9] The slight enhancement of the cerebrospinal fluid (CSF) on hT_2-FL images acquired 4 h after a single dose of IV-GBCA had been reported in healthy subjects with normal renal function[10]; however, the enhancement of the PVS in healthy subjects has not been reported previously. The enhancement of the PVS, though, has been reported in a patient with renal insufficiency.[11] The PVS represents an entrance point to the glymphatic system, a recently discovered macroscopic waste clearance system of the brain.[12,13]

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This was observed in all 8 healthy subjects and all 19 patients
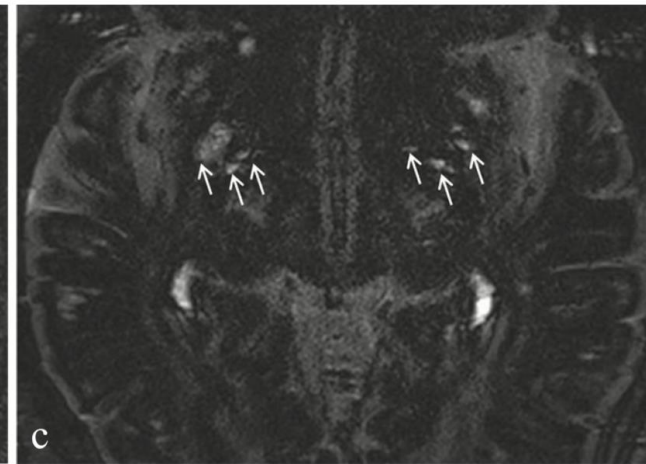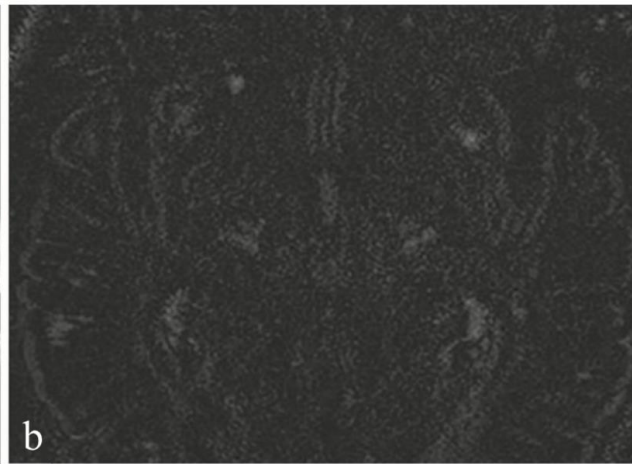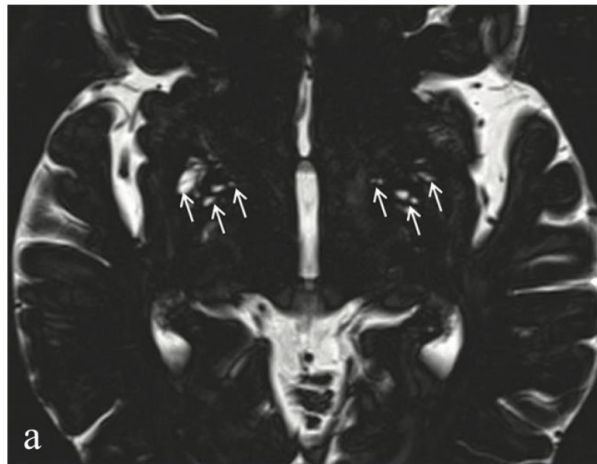
Pre GBCA
T2WI

Pre GBCA
FLAIR

4 hour
post GBCA
FLAIR

Conclusion

The enhancement of the PVS at 4 h after a single dose of IV-GBCA was confirmed in human subjects without renal insufficiency. This might represent the

Pre-clinical evaluation of gadobutrol: a new, neutral, extracellular contrast agent for magnetic resonance imaging

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Abstract

The Gd^{3+}-complex of 10-(2,3-dihydroxy-1-hydroxymethylpropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid (gadobutrol) is a new, neutral Gd-chelate for use as an extracellular contrast agent in magnetic resonance imaging (MRI). The Gd blood level in dogs after intravenous (i.v.) injection decreased with a terminal half-life of about 45 min, the clearance was about 3.75 ml/min per kg and the distribution volume of 0.23 l/kg suggested an extracellular distribution. Biodistribution experiments in rats revealed that only a very small amount (0.16%) of the dose was left in the body 7 days after i.v. injection. Measurable amounts of Gd could be detected only in the liver, kidneys and bones. The osmolality (0.57 osmol/kg at 0.5 mol/l and 1.39 osmol/kg at 1 mol/l) is in the range of other low osmolality contrast media for MRI. Only very little interaction with biologically relevant molecules was suggested by a histamine release test and a lysozyme inhibition test. An i.v.-LD_{50} of 23 mmol/kg in mice combined with a comparatively high T_1-relaxivity (5.6 l/mmol per s at 0.47 T and 6.1 l/mmol per s at 2 T) in plasma promises a high margin of safety. In preliminary imaging experiments, gadobutrol caused high enhancement in different lesions (cerebral infarct, brain tumor) of the rat. Tripling of the typical clinical dose of 0.1 mmol/kg was shown to provide additional diagnostic gain in lesions of this type.

Keywords: Contrast media, MR; Magnetic resonance (MR), contrast media

1. Introduction

In many millions of applications since its launch in 1988, Magnevist®, the first contrast medium for magnetic resonance imaging (MRI), has proven its efficacy and its excellent tolerance; it is even superior to that of the nonionic X-ray contrast media [1]. The rate of adverse reactions caused by contrast media is due to a number of factors, of which the osmotic load is one of the most important. Physiologic problems, such as crenation of erythrocyes, vasopressin release, and changes in the circulatory system are related to it [2,3]. For the normal clinical dose (0.1 mmol/kg) the osmotic load in the case of the ionic MRI contrast media like Magnevist® is much lower than that of the ion-ionic X-ray contrast media, at least by a factor of two. Therefore, a switch from ionic to non-ionic MRI contrast media should scarcely be measurable with regard to tolerance, whereas it was a clear improvement in the case of the X-ray contrast media [4]. However, assuming that a much higher dose is diagnostically useful and desirable in some cases, as reported elsewhere [5], the problem of the osmolality of MRI contrast media, again, may take on a greater significance. Independently from this, a further reduction of adverse events caused by other factors than osmolality seems to be desirable. The Gd^{3+}-10-(2,3-dihydroxy-1-hydroxymethylpropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid (gadobutrol) is a new, neutral gadolinium complex in-

* Corresponding author, Tel.: +49 30 34989118; Fax: +49 30 34989429.

Table 6

LD$_{50}$ and ED$_{50}$ of different contrast media after intracisternal application in rats

	LD$_{50}$		ED$_{50}$	
	Median value (μmol per kg)	Confidence interval ($P < 0.05$)	Median value (μmol per kg)	Confidence interval ($P < 0.05$)
Gadobutrol	86	64–115	18	8–33
ProHance®	46	34–62	20	8–29
Dotarem®	58	43–78	31	19–44
Omniscan®	208	149–308	47	22–86
Magnevist®	740	480–1250	73	33–165

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Gadolinium Encephalopathy After Intrathecal Gadolinium Injection

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From: Penn State Hershey Medical Center, Hershey, PA

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Medical Director, Spine Center
Co-Director, Pain Medicine Fellowship Program
Hershy, PA
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Background: Gadolinium-induced encephalopathy is a well documented complication due to the inadvertent entrance of a high dose of gadolinium into the intrathecal compartment. In lab animals, injecting gadolinium into the intrathecal compartment resulted in neurotoxicity and seizures. It is also well recognized that the presence of autologous blood in the intrathecal compartment can cause a broad range of neurological changes that can include seizures and mental status changes. At the time of writing this report, there were no references in the literature of simultaneous injection of gadolinium and blood into the subarachnoid space.

Case: We present a case of a patient who received a high dose of gadolinium in the epidural space for needle placement confirmation during a fluoroscopically-guided epidural steroid injection for the treatment of lumbar radiculopathy. The injection was complicated by a wet tap necessitating an epidural blood patch for post-dural puncture headache. Shortly after the injection of the autologous blood, the patient developed grand-mal seizures and mental status changes requiring endotracheal intubation and admission to an intensive care unit. We describe the clinical course and management, as well as brain MRI findings and cerebrospinal fluid (CSF) changes. The patient made a complete recovery and was discharged.

Conclusion: This case reinforces the need for using a low dose of gadolinium for the confirmation of needle placement in the epidural space, especially in procedures that carry the risk of inadvertent intrathecal injection. We attribute these findings to inadvertent simultaneous intrathecal injection of high dose gadolinium and autologous blood. A literature review of the cases of gadolinium-induced encephalopathy is provided followed by discussion.

Key words: Postdural puncture headache, epidural blood patch, intrathecal gadolinium, seizures, mental status changes, encephalopathy

A 61-year-old Caucasian female with a history of chronic lumbar radiculopathy and right lower extremity radicular pain received an epidural steroid injection (ESI) at a community-based outpatient pain clinic. The first attempt was executed at the L4-L5 interspace using a 15 cm epidural needle (gauge unknown) under fluoroscopic guidance utilizing loss-of-resistance technique. It was complicated by a "wet tap," and the needle was subsequently withdrawn. A second attempt at the L5-S1 interspace was successful. Due to a documented history of iodine allergy, a total of 4 mL [1,148 mg gadodiamide (287 mg/ml gadodiamide)] of non-iodine containing contrast, gadolinium (Omniscan), was injected into the epidural space, which was confirmed on an epidurogram in biplanar views. A 9 mL solution containing 2 mL/80mg of Depo-Medrol diluted in 7 mL of preservative-free normal saline (presumably for better spread) was

Neurotoxic Potential of Gadodiamide after Injection into the Lateral Cerebral Ventricle of Rats

David E. Ray, Janice L. Holton, Christopher C. Nolan, John B. Cavanagh, and Ernest S. Harpur

PURPOSE: Results of a previous report showed that, if administered by intraventricular injection to access tissue normally protected by the blood-brain barrier, gadopentetate dimeglumine produced acute excitation, persistent ataxia, and widespread brain lesions in rats at 5-μmol/g brain but not at 3.8-μmol/g brain. The present study using gadodiamide was undertaken to see whether the effects were agent-specific.

METHODS: Rats, surgically prepared with a lateral ventricular cannula, were administered a slow injection at 2 μL/min of gadodiamide into the lateral ventricle, and behavioral and neuropathologic changes were noted.

RESULTS: Both gadodiamide and gadopentetate dimeglumine produced focal and generalized myoclonus over several hours. Gadodiamide did not produce the medium-term tremor or persistent ataxia seen after treatment with gadopentetate dimeglumine. Neuropathologic changes developed over 1 to 3 days and took three distinct forms: vacuolated thalamic lesions closely resembling those produced by gadopentetate dimeglumine; small but similar vacuolated symmetrical caudate lesions not produced by gadopentetate dimeglumine; and severe swelling and astrocytic hypertrophy and hyperplasia in the cerebellar vermis, again not produced by gadopentetate dimeglumine. Unlike gadopentetate dimeglumine, gadodiamide produced no spinal cord lesions. The cerebellar changes were seen at 1.25-μmol/g brain and above, behavioral changes at 2.5-μmol/g brain and above, and thalamic and caudate lesions at 10-μmol/g brain, the maximal dose used. Markedly reducing the rate of injecting the same volume over 28 hours prevented the acute excitation but did not reduce the severity of the morphologic effects.

CONCLUSION: The acute excitatory effects of high intraventricular doses of gadopentetate dimeglumine and gadodiamide are similar and appear to be attributable to local action at the infusion site, but differences exist between the two agents in the character and topography of the distant morphologic changes. The cerebellum was the brain area most sensitive to gadodiamide in this experimental model. It is unlikely that gadodiamide would gain access to the brain at these tissue doses when used intravenously for conventional clinical imaging, but our experimental model suggested that it had some unexpectedly specific neuropathologic potential.

A number of pharmacologic compounds are used clinically in conditions in which the permeability of

the blood-brain barrier is increased, notably agents for brain imaging and for antibiotic and anticancer purposes. These agents, therefore, gain access to brain tissue to an extent not possible either in healthy individuals or in healthy experimental animals used for toxicity testing. Consequently, several experimental methods have been used in attempts to assess the direct neurotoxic potential of such agents, notably osmotic opening of the blood-brain barrier (1), intrathecal dosing (2, 3), and in vitro systems using brain sections (4) or cell cultures (5). Extensive clinical use has shown modern MR imaging agents to be well tolerated in their many applications (6, 7), including use in a large number of patients with a compromised blood-brain barrier. Previous investigations, however, have reported that gadopentetate dimeglumine may

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Interpretation of the significance of the cerebellar lesion is made difficult by the seemingly unique nature of the cellular response. The apparently reactive nature of the astrocytic lesion (10, 11) led us to look for primary damage elsewhere, but, with the exception of minor swelling of Purkinje cell dendrites and some late granule cell pyknosis seen at high doses, no evidence of such damage could be discerned. Lack of neuronal damage in the early stages is supported by the lack of any microglial reaction. The early appearance of electron-dense multilamellar bodies within the end-feet and processes of Bergmann glial cells may have resulted from the phagocytosis of material from the extracellular space, but we have been unable to detect gadolinium within the bodies by X-ray diffraction analysis. Restriction of the changes to the vermal and paravermal regions of the cerebellum is a feature that has been found with other agents that enter the CSF either in disease or by experimental design, such as alcoholic cerebellar disease (12, 13) and superficial siderosis of the CNS (14). It is also

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intraventricularly. The capacity of cerebellar cortical astrocytes and the dendrites of Purkinje cells to take up materials from the CSF, and the relatively large volume of CSF in the subarachnoid spaces overlying the vermis of the cerebellum, should both be considered as likely factors in this localization. It is possible

emia in the rat (20). We suggest, therefore, that the early astroglial response seen at 3 days in the present study, when multilamellar bodies were numerous in their cytoplasm, may have been the direct response to the incorporation of the gadolinium compound from the extracellular space.

Persistence of Gadolinium Contrast Enhancement in CSF: A Possible Harbinger of Gadolinium Neurotoxicity?

Gadolinium chelates are relatively safe agents, with occasional hypersensitivity reactions and systemic toxicity with predominantly extracellular distribution and primarily glomerular clearance. Neurotoxicity has been estimated at approximately 1% on initial studies regarding the pharmacokinetics of gadolinium.[1]

We recently encountered a patient who, after receiving MR imaging and contrast MR angiography for a syncopal work-up, became encephalopathic. A follow-up MR imaging showed homogeneous T1 shortening and fluid-attenuated inversion recovery hyperintensity in the CSF (Fig 1). Lumbar puncture performed at that time yielded CSF that also demonstrated T1 shortening. Mass spectrometry yielded a concentration of 23,000 nmol/mL of gadolinium. The patient improved after serial hemodialysis sessions to baseline.

During interpretation of the second MR imaging, we recalled a similar report by Maramattom et al,[2] who described a 57-year-old woman with end stage renal failure, who developed encephalopathy after repeated intravenous gadolinium-enhanced MR imaging. On the basis of the temporal relationship of the gadolinium chelate administration and the resolution after dialysis, they suggested a diagnosis of gadolinium-related encephalopathy.[2] The authors measured CSF gadolinium levels at 28,591 ng/mL (50 nmol/mL). CSF gadolinium-related T1 shortening in the setting of renal failure was initially reported by Rai and Hogg,[3] who emphasized the need for familiarity with this appearance, lest it be confused with other pathologic conditions.

In 2007, Arlt and Cepek[4] described a more dramatic example of neurotoxicity in a 64-year-old woman with presumed spinal stenosis who inadvertently received 20 mL of intrathecal gadolinium dimeglumine (10 mmol), which resulted in ataxia and delirium. They measured a CSF concentration of gadolinium of 23,365 nmol/mL on day 1, which diminished to undetectable levels by day 5.

In our patient, the paramagnetic effects in the patient's CSF also likely resulted from accumulation of gadolinium chelate administered during the initial MR imaging. Ultimately, the working diagnosis of gadolinium neurotoxicity was made because no other causes for the patient's encephalopathy were discovered. Although it is known that inorganic gadolinium salts are neurotoxic, it is unclear whether the unchelated gadolinium atoms, gadolinium chelates, or the chelating agents are the culprits for neurotoxicity.

Recent reports of neurotoxicity associated with gadolinium contrast should draw renewed attention to potential, though rare, adverse affects. When diffuse T1 shortening of the CSF is encountered, we suggest that this observation should prompt inquiry as to the patient's
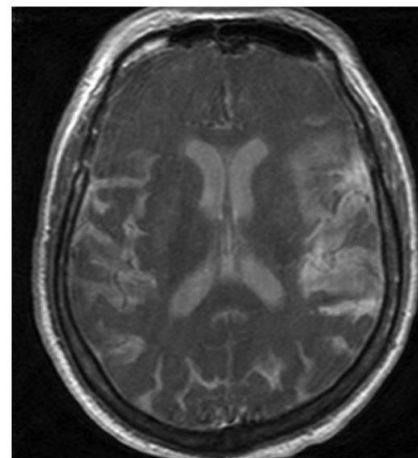

Fig 1. T1 precontrast MR image shows homogenous T1 shortening in the CSF.

renal status and discussion with the clinical team, who may be unaware of gadolinium-associated encephalopathy. Subclinical neurotoxicity may escape clinical attention if patients with renal failure are not specifically monitored, especially because gadolinium is efficiently removed by dialysis (95% at 3 sessions).[1] We suggest that caution should be exercised when contemplating administering gadolinium chelates in this population due to diffusion of gadolinium chelates into the CSF and possible subsequent neurotoxicity.

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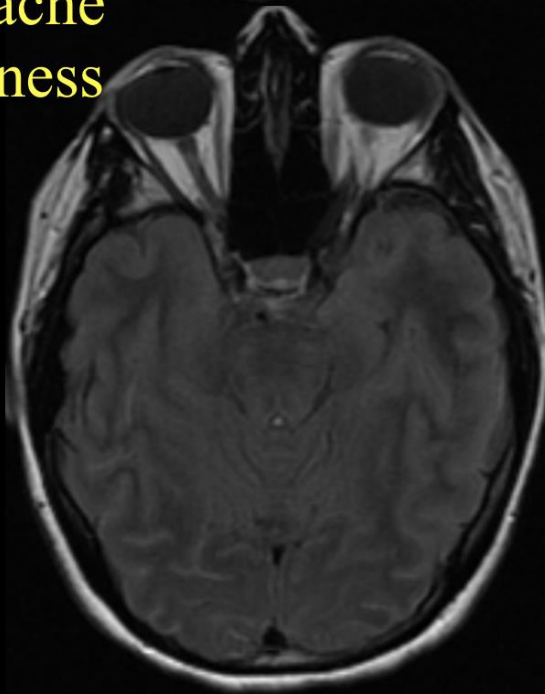
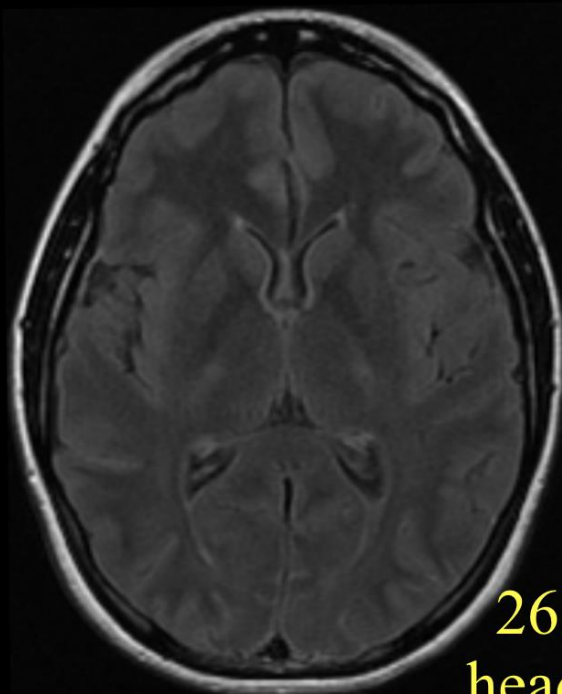Pre-contrast
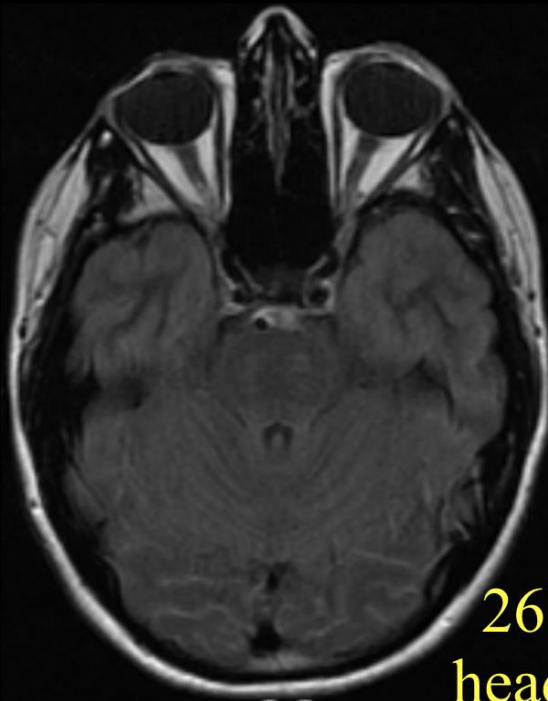
1 hour
post contrast
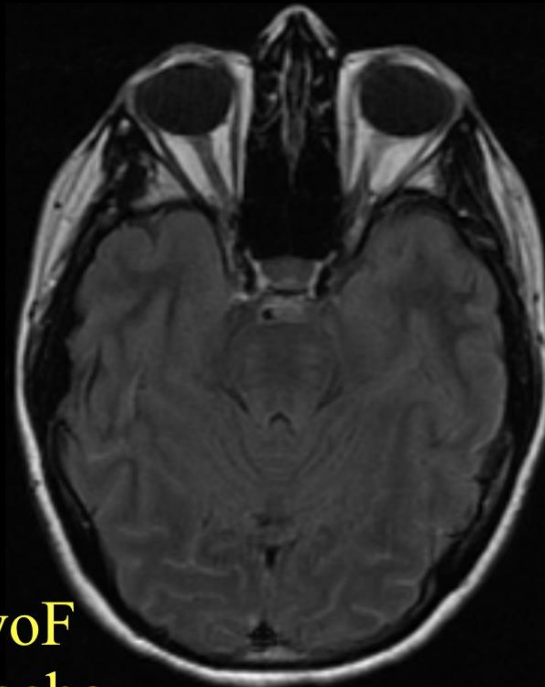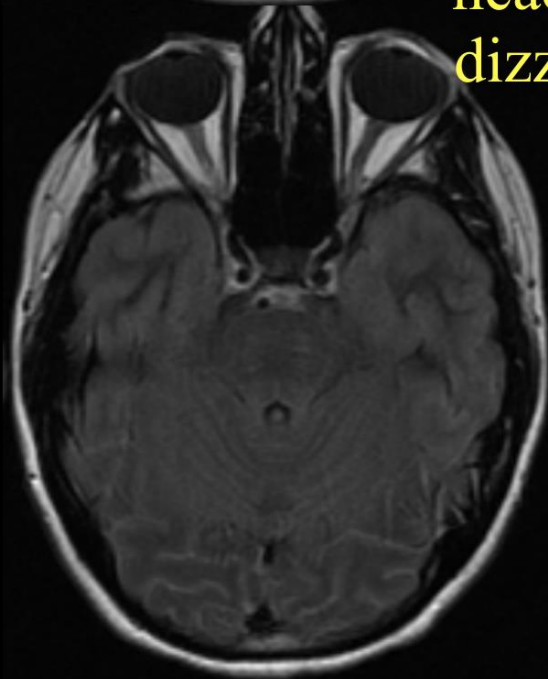
26 yoF
headache
dizziness

2 hours
post contrast

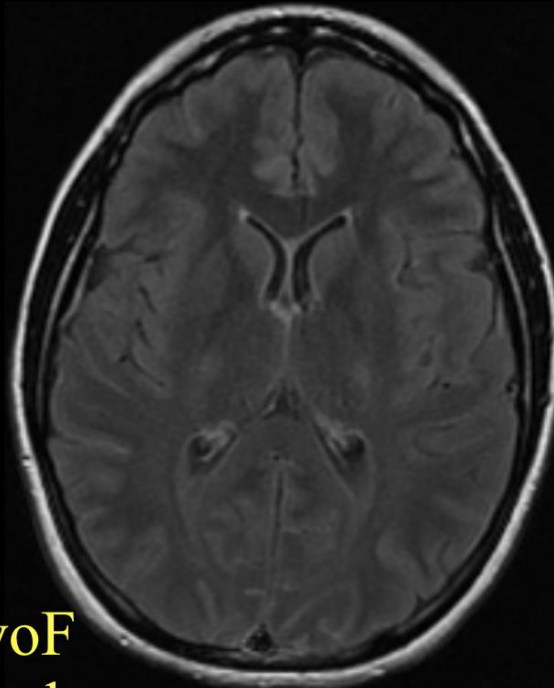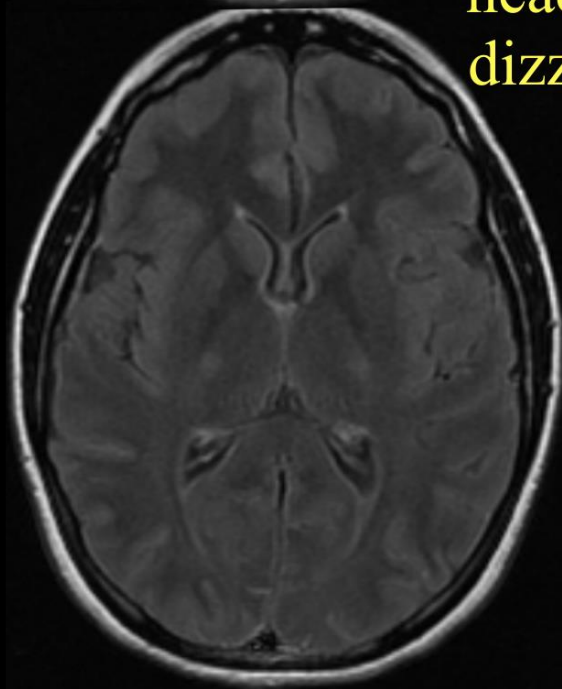7 hours
post contrast
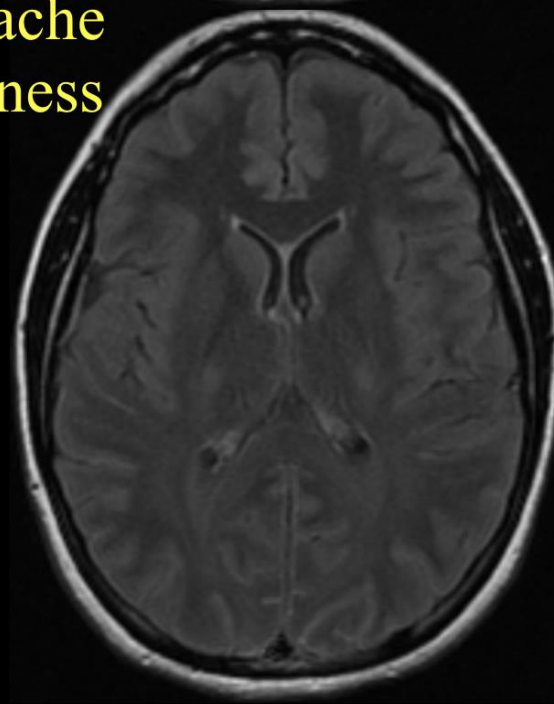
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Pre-contrast

1 hour
post contrast

26 yoF
headache
dizziness

2 hours
post contrast

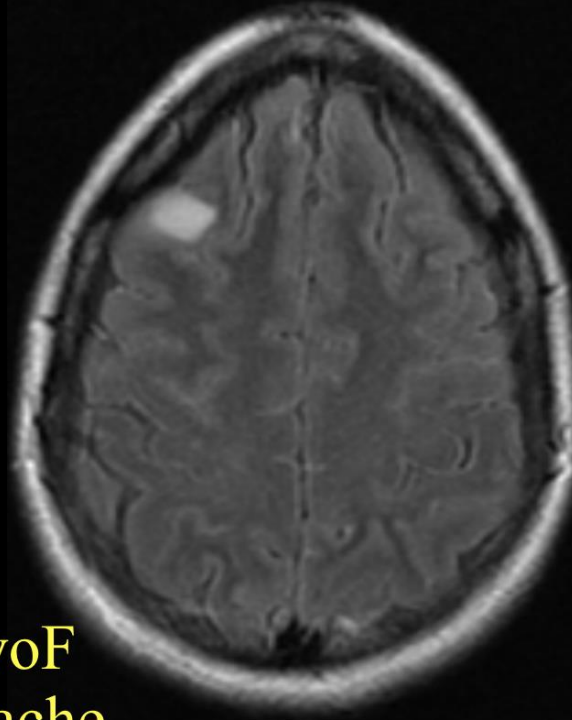7 hours
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Kanal Gd -> Brain?

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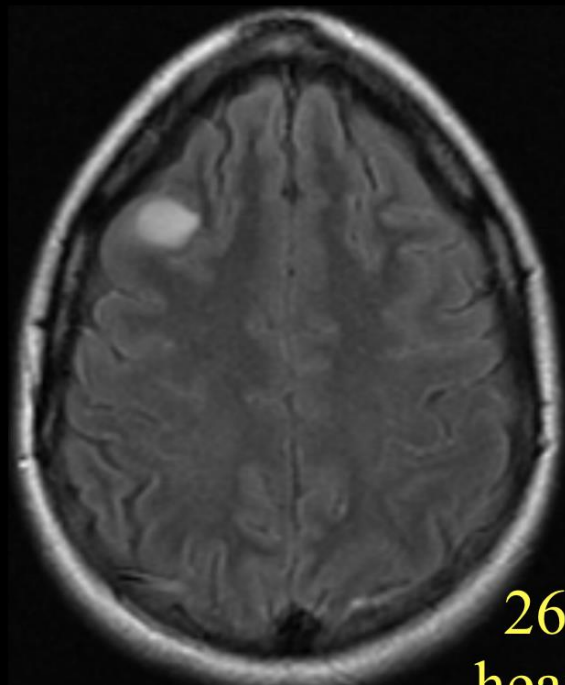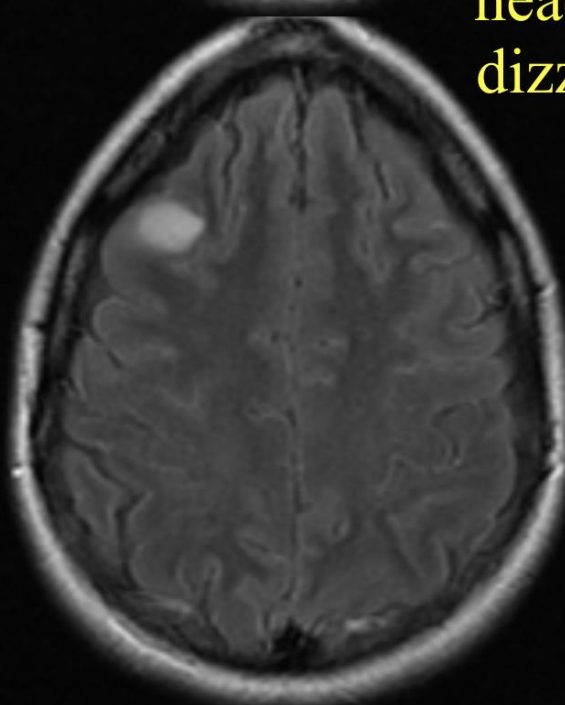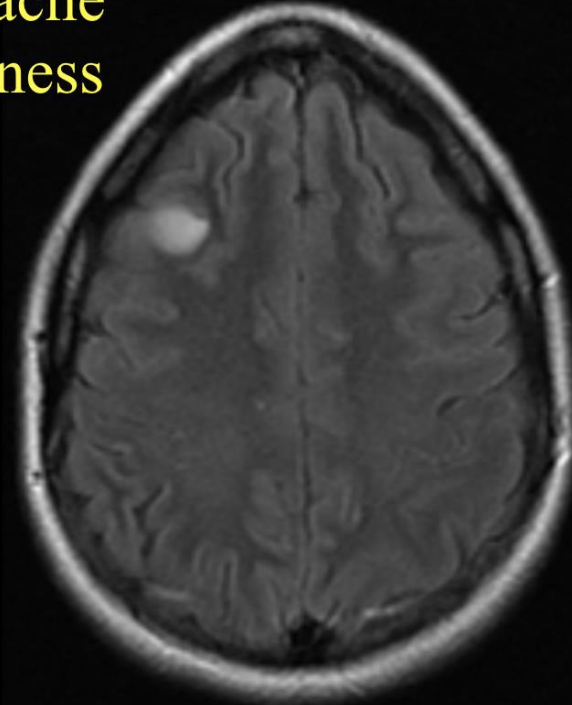
Objectives: There have been recent studies evaluating brain magnetic resonance imaging changes in patients with normal renal function, after intravenous administration of gadolinium-based contrast agents (GBCAs). Their findings were supported by histological evidence as well and brought a new vision concerning what needs to be learned to provide better patient care. In this report, we aim to present brain magnetic resonance imaging changes after intrathecal administration of a linear ionic agent (gadopentetate dimeglumine).

Materials and Methods: We evaluated hyperintensities in the deep nuclei of the brain in 6 patients with normal renal function after intrathecal administration of a linear ionic GBCA, without other confounding intravenous GBCA administrations. For visual analysis, T1 signal hyperintensity of the globus pallidus (GP), putamen, pons, and dentate nucleus (DN) were scored on a 4-point scale. For quantitative analysis, using the unenhanced T1-weighted images oval regions of interests were placed within the DN, central pons, GP, and thalamus on different image slice positions.

Results: On visual analysis, 5 patients had T1 signal hyperintensity of the DN and GP, whereas the DN/pons signal intensity and the GP/thalamus signal intensity were found to be increased in all 6.

Conclusions: This observation not only adds to our fund of knowledge concerning biodistribution and pharmacokinetics of those agents, but also raises the question of a possible association with the glymphatic pathway.
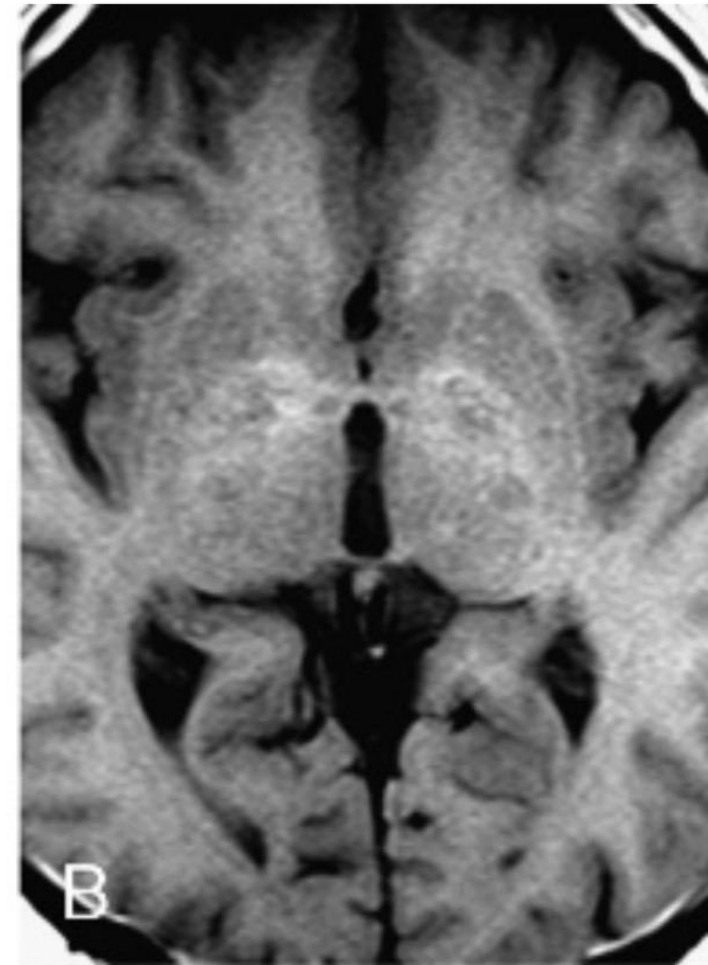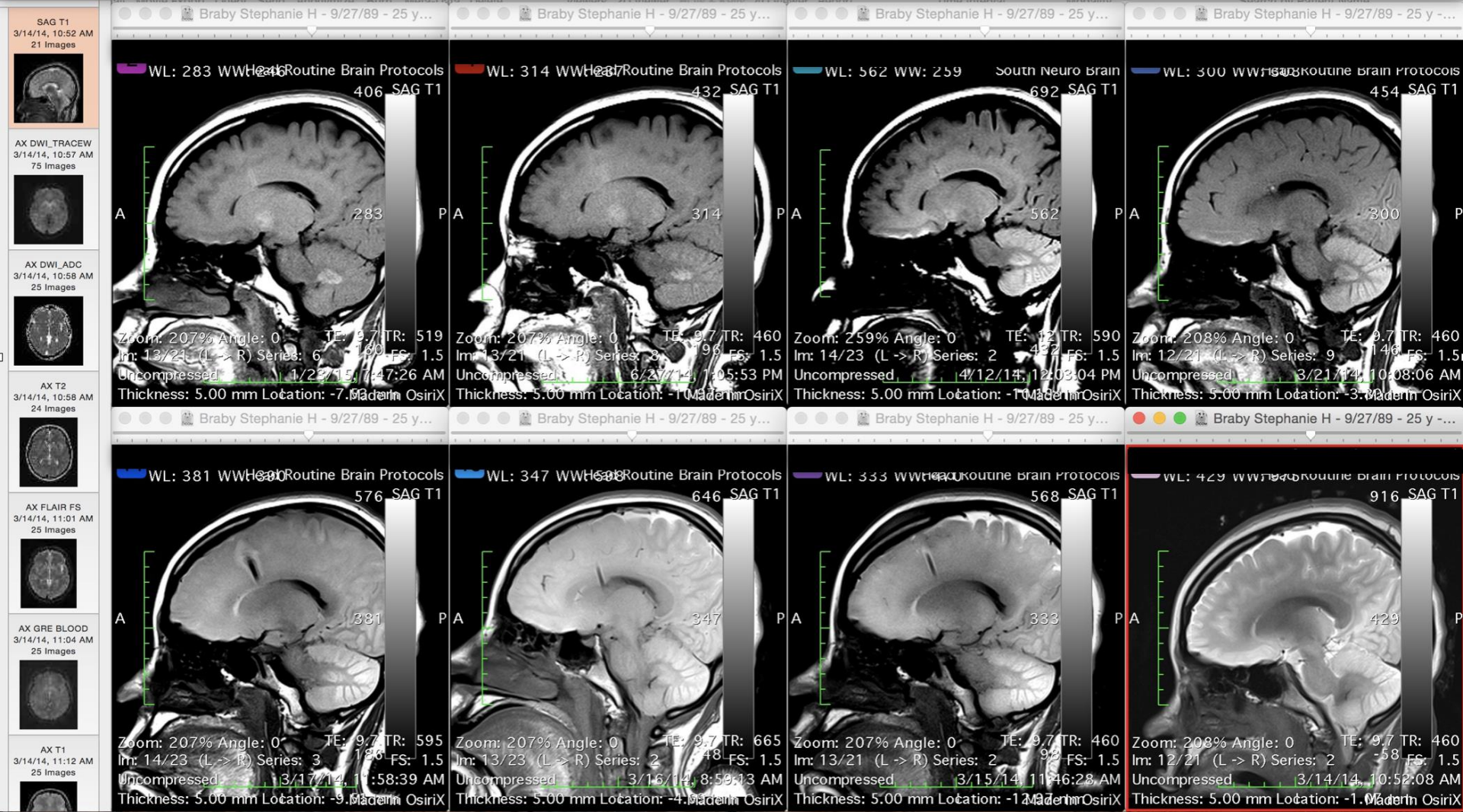
FIGURE 2. MRI scans of a 49-year-old patient with a history of CSF leakage. Unenhanced T1-weighted axial images shows marked high signal intensity in the dentate nucleus (A) with a less prominent signal increase in globus pallidus (B).

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Blood–ocular barrier disruption in acute stroke patients

Emi Hitomi, BS, Alexis N. Simpkins, MD, PhD, Marie Luby, PhD, Lawrence L. Latour, PhD, R. John Leigh, MD, and Richard Leigh, MD

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Abstract

Objective
Prompted by the unexpected finding of gadolinium leakage into ocular structures (GLOS) in acute stroke patients, we studied the frequency and nature of this finding in 167 patients.

Methods
Patients were selected who had an MRI with gadolinium at baseline and another MRI with fluid-attenuated inversion recovery (FLAIR) imaging at 2 and/or 24 hours later. GLOS was detected as lack of vitreous and/or aqueous fluid suppression on postcontrast FLAIR images.

Results
GLOS, evident on postcontrast FLAIR MRI, occurred in 127/167 (76%) patients: 86/109 (79%) patients treated with tissue plasminogen activator and 41/58 (71%) who were untreated. At 2 hours after administration of the contrast, GLOS was more common in the aqueous chamber alone, occurring in 67% of patients, compared to the vitreous chamber alone, seen in 6% of patients; it occurred in both chambers in 27% of patients. At 24 hours, GLOS was present in 121/162 (75%) patients, always involving the vitreous chamber, but also affecting the aqueous chamber in 6% of cases. Vitreous GLOS at 24 hours was associated with increasing age ($p = 0.002$) and a higher burden of cerebral white matter hyperintensities ($p = 0.017$). Patients with rapid diffuse GLOS, defined as GLOS involving both chambers at 2 hours, had larger infarcts ($p = 0.022$) and a higher degree of blood–brain barrier permeability ($p = 0.025$).

Conclusions
We found GLOS to be common in patients with acute stroke; delayed GLOS was a marker for chronic vascular disease. The mechanism for acute GLOS remains uncertain but may be a remote effect of acute cerebral injury on the blood–ocular barrier.
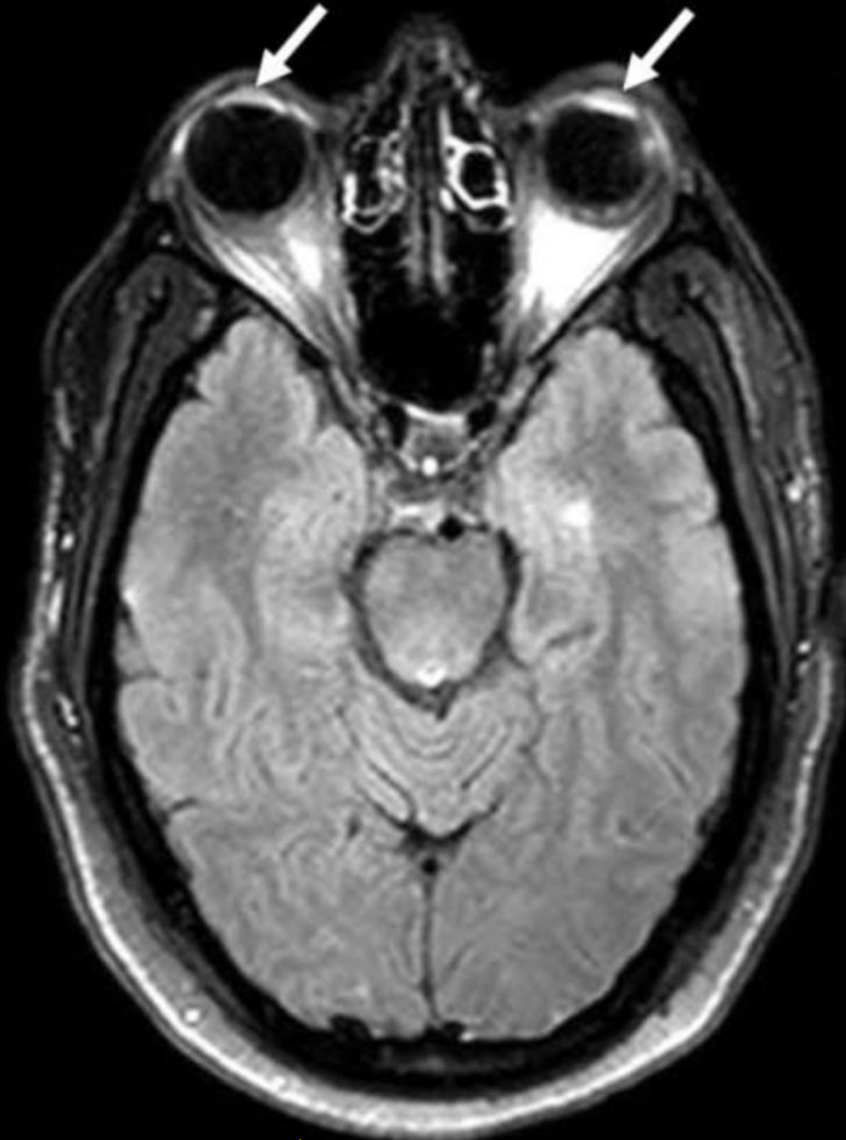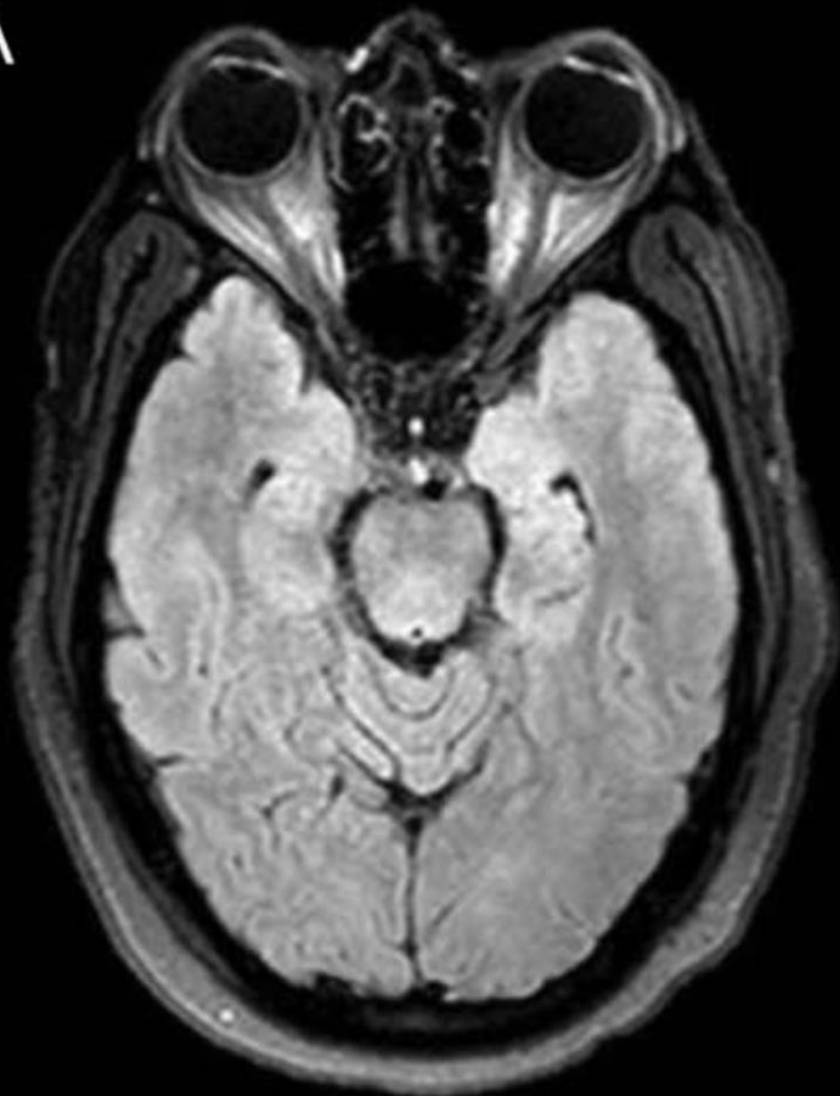
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Editorial
Blood–ocular barrier leakage: Further evidence for remote effects following ischemic stroke

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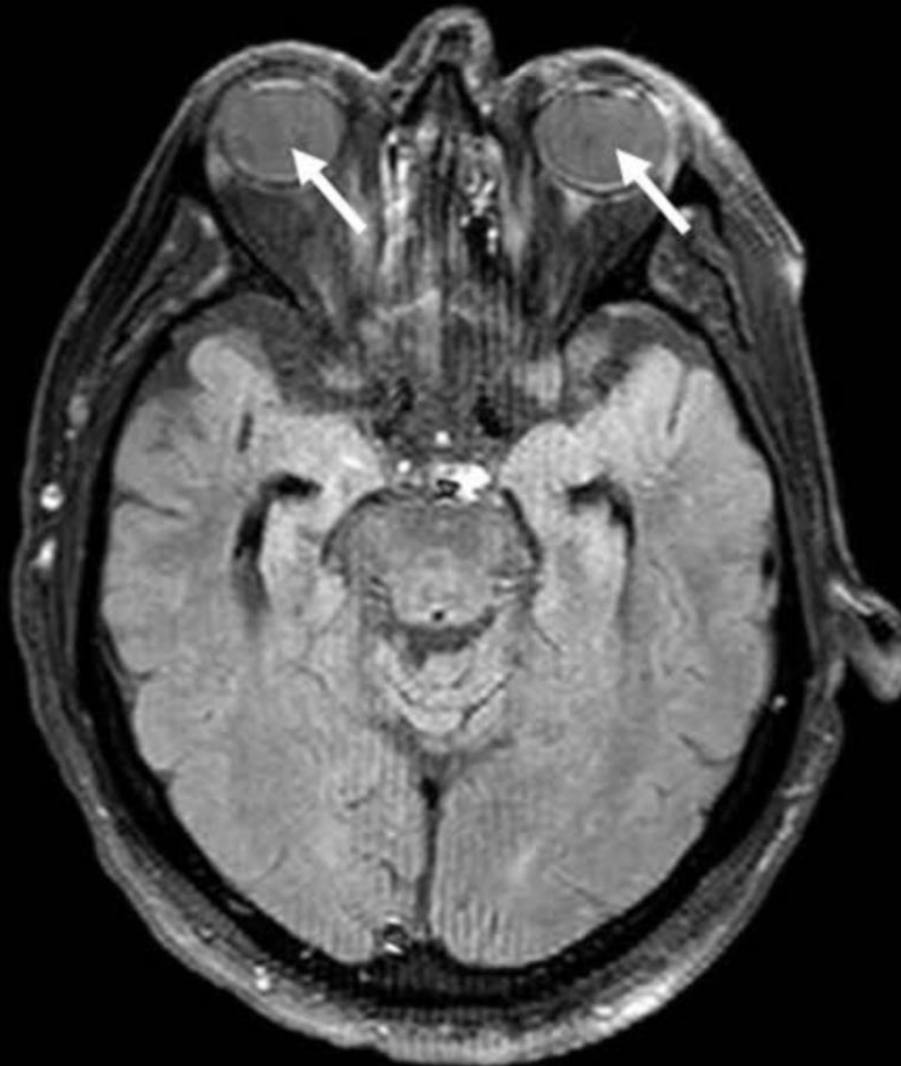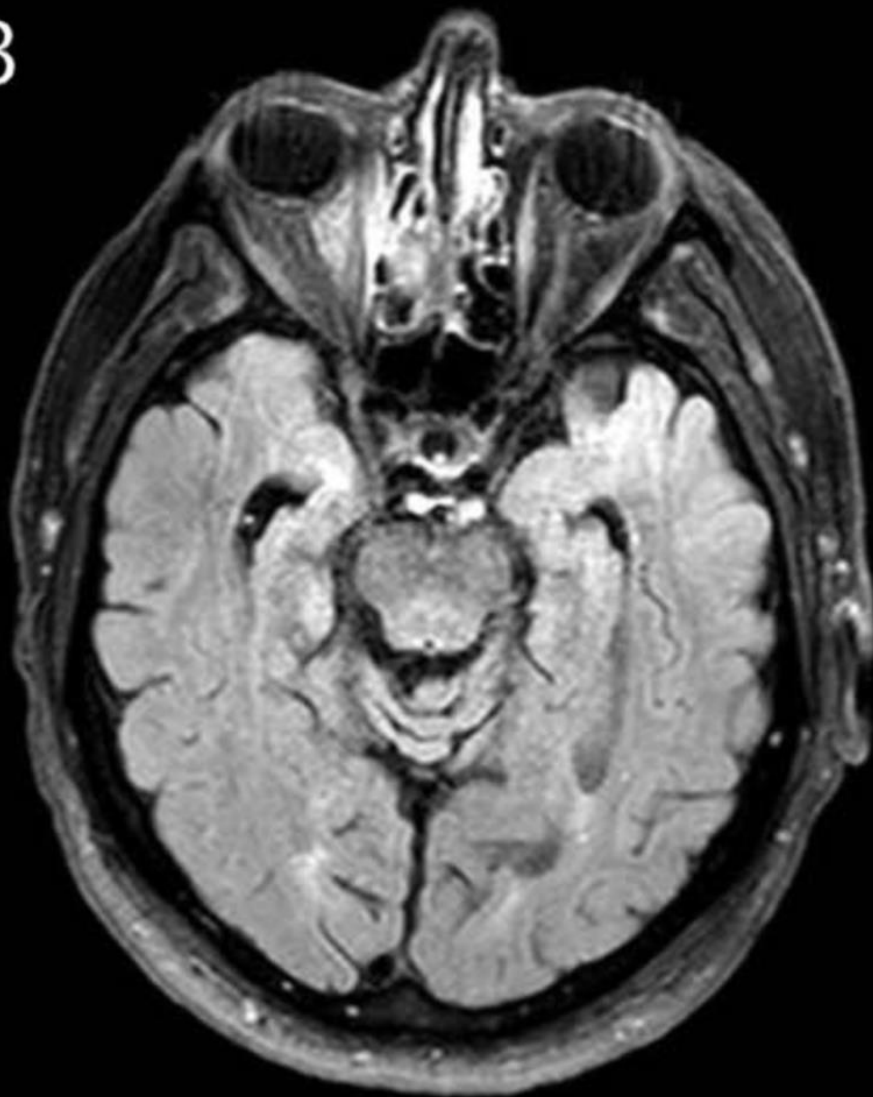Gd -> Brain?

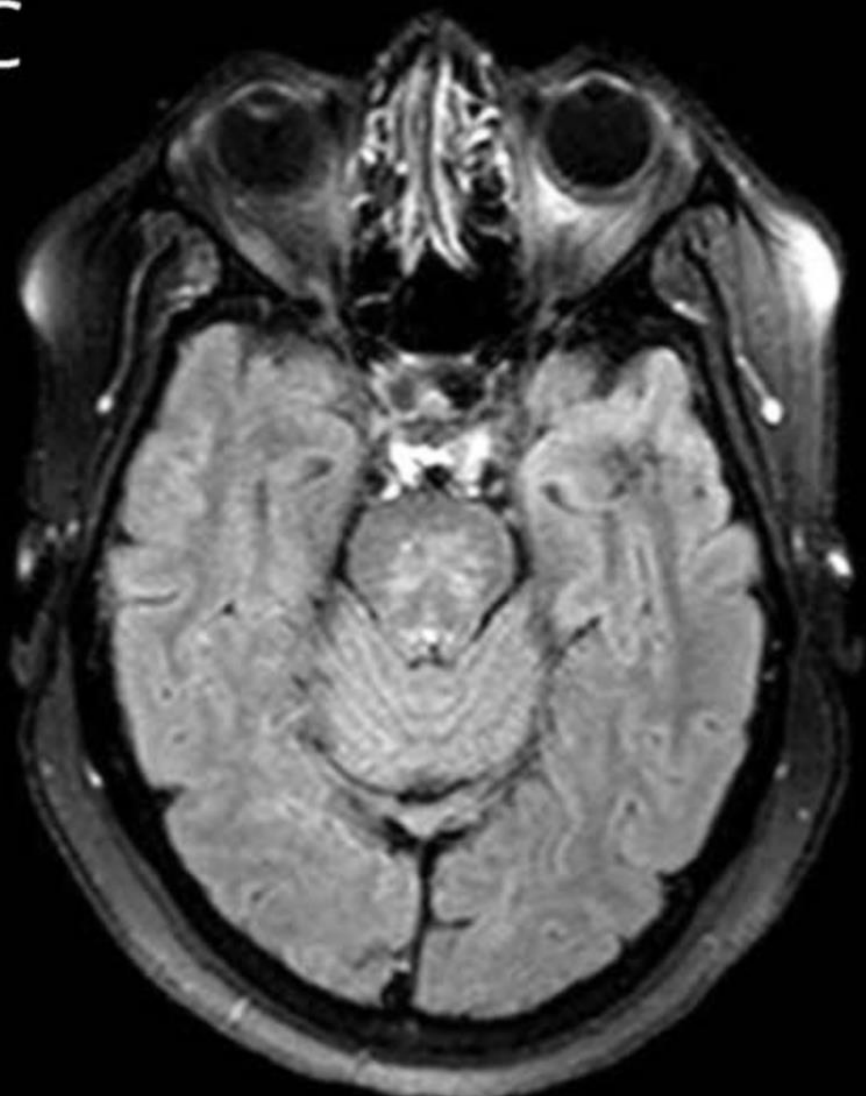Pregadolinium

Postgadolinium

A

Aqueous humor only

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Pregadolinium

Postgadolinium

Vitreous humor only

Kanal Gd -> Brain?

Pregadolinium

Postgadolinium

C

Aqueous and Vitreous humor

Kanal Gd -> Brain?

How Does Gadolinium Enter the Brain?

Gadolinium in the CSF

A) Gadolinium chelates in the CSF are clearly neurotoxic (animals and human data); macrocyclic GBCA are MORE neurotoxic than are linear ones when introduced directly into the CSF

B) Gadolinium is found in the CSF of patients with renal disease hours after intravenous administration

C) Gadolinium has been found in the CSF hours after intravenous administration even in patients with normal renal function

   i) It may be significant that NOT all patients necessarily show gadolinium in the CSF - or at least not to the same degree - following intravenous administration. Could this play a role in how much is retained and/or, if an association is found with symptomatology claims, who becomes symptomatic?

How Does Gadolinium Enter the Brain?

Gadolinium in the CSF

D) Gadolinium is also found in the CSF of patients with parenchymal pathology

E) Gadolinium can also be found in the globes of at least some patients shortly after intravenous administration

F) The perivascular distribution of much of the gadolinium found on autopsy and histology suggests that VR spaces/glymphatics may be a likely pathway for intracranial gadolinium deposition

How Does Gadolinium Enter the Brain?

Gaps in knowledge

A) What is the molecular speciation of the gadolinium found in the CSF (and globe) following intravenous administration for *each* GBCA (as oppose to by "class")?

B) In patients without intracranial or meningeal pathology, how does gadolinium get into the CSF (and aqueous/vitreous humor) following intravenous injection?
>   i) Via the choroid plexus?
>   ii) Via the meningeal surfaces?

C) Can any of these pathways be blocked?

How Does Gadolinium Enter the Brain?

Gaps in knowledge

    D) What are the relative neurotoxicities, if any, for intact GBCA gadolinium-ligand chelates versus insoluble gadolinium forms (e.g., gadolinium phosphate) versus gadolinium bound to/interacting with macromolecules?

    E) Consider the possibility that insoluble gadolinium may lead to fibrosis in the skin but as the brain does not heal with fibrosis but rather gloss, what may be a toxic form of gadolinium in the skin or elsewhere in the body may be non-toxic or inert in the brain (e.g., calcification of the basal ganglia).