

High signal intensity in dentate nucleus and globus pallidus on unenhanced T1-weighted MR images in three patients with impaired renal function and vascular calcification

Sebastiano Barbieri^a, Christophe Schroeder^a, Johannes M. Froehlich^a,
Andreas Pasch^b and Harriet C. Thoeny^{a*}

Gadolinium-based contrast agents (primarily those with linear chelates) are associated with a dose-dependent signal hyperintensity in the dentate nucleus and the globus pallidus on unenhanced T1-weighted MRI following administration to selected patients with normal renal function. The accumulation of gadolinium has also been reported in the skin, heart, liver, lung, and kidney of patients with impaired renal function suffering from nephrogenic systemic fibrosis (NSF). Here we report on three patients with impaired renal function and vascular calcification (two with confirmed NSF) whose unenhanced T1-weighted MRIs showed conspicuous high signal intensity in the dentate nucleus and the globus pallidus after they had been exposed to relatively low doses of linear gadolinium-based contrast agents (0.27, 0.45, and 0.68 mmol/kg). Signal ratios between dentate nucleus and pons and between globus pallidus and thalamus were comparable with previously reported measurements in subjects without renal impairment. Of note, all three analysed patients suffered from transient signs of neurological disorders of undetermined cause. In conclusion, the exposure to 0.27–0.68 mmol/kg of linear gadolinium-based contrast agent was associated with probable gadolinium accumulation in the brain of three patients suffering from impaired renal function and vascular calcification. © 2016 The Authors. *Contrast Media & Molecular Imaging* published by John Wiley & Sons Ltd.

Keywords: gadolinium-based contrast agent; dentate nucleus; globus pallidus; nephrogenic systemic fibrosis; calciphylaxis

1. INTRODUCTION

Gadolinium-based contrast agents (GBCA) are used in magnetic resonance imaging (MRI) to accentuate differences in signal intensity between adjacent normal and abnormal tissues. Thus, they improve detection and characterization of pathophysiological processes (1).

Since gadolinium (Gd^{3+}) in its free form is cytotoxic, it is contained in GBCAs as a central moiety of aminopolycarboxylic acid ligands (2). GBCAs are administered intravenously and were thought to be excreted, as intact compounds, in a rapid and complete manner (3).

In 2006, an association between the administration of GBCA and the development of nephrogenic systemic fibrosis (NSF) in patients with pre-existing renal dysfunction was established (4). Shortly after, gadolinium was detected in the skin (5), heart (6), liver, lung, and kidney (7) of NSF patients who had been exposed to GBCAs. Gadolinium deposition has also been reported in the cerebellum (7) but, since it was detected only in perivascular glial cells, it was generally believed that GBCAs do not cross the blood-brain barrier. In addition, signs associated with NSF generally concern the skin, joints, and internal organs and not the brain.

The amount of gadolinium deposition in tissues is likely linked to whether the GBCA complex remains stable in a biological environment, thus preventing the dechelation of gadolinium ions. Commercially available GBCAs are either linear or macrocyclic, depending on the chemical structure of the chelator. Moreover, the sum of positive and negative charges (ionicity) of the complex influences its thermodynamic stability. Evidence suggests

that linear GBCAs are generally less stable and might result in increased gadolinium deposition in the brain compared with macrocyclic GBCAs (8,9).

Current guidelines in Europe recommend administering the smallest required amount of macrocyclic GBCA or of gadobenate dimeglumine (a linear GBCA) to patients with a low estimated glomerular filtration rate (GFR) (10). As a consequence, the incidence of NSF has nearly vanished (11). However, several recent studies have established that GBCAs (primarily those with linear chelates) are associated with a dose-dependent relative signal hyperintensity in the dentate nucleus and the globus pallidus on unenhanced T1-weighted MR images following administration to selected subjects with normal renal function (12–14). Most patients

* Correspondence to: H. C. Thoeny, MD, Inselspital, Freiburgstrasse 10, CH-3010 Bern, Switzerland. E-mail: Harriet.Thoeny@insel.ch

a S. Barbieri, C. Schroeder, J. M. Froehlich, H. C. Thoeny
Institute of Diagnostic, Pediatric, and Interventional Radiology, University Hospital Bern (Inselspital), Bern, Switzerland

b A. Pasch
Department of Clinical Chemistry, University Hospital Bern (Inselspital), Bern, Switzerland

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analysed in these retrospective studies had a history of neoplastic disease or multiple sclerosis without targeted or whole-brain radiation therapy. Histological analyses confirmed that the high signal intensity in these brain regions is due to the presence of gadolinium (15,16).

Histological analyses also indicated that gadolinium is detected in higher amounts in subcutaneous tissue adjacent to vessels and within vascular walls, especially in the presence of calcifications (independent of whether the patient had normal or impaired renal function) (7,17,18). Calcification and non-specific fibrosis are frequent findings in patients with chronic renal failure with or without NSF (7). Here we report on three patients with impaired renal function and vascular calcification who were repeatedly exposed to GBCA and received brain MRIs at our institution due to episodes of impaired consciousness. Two of these patients had NSF; at the time the causal association between GBCA exposure and NSF was not known.

2. CASES

2.1. Patient 1

2.1.1. 52 year-old Caucasian female

Reflux nephropathy led to chronic kidney disease and kidney transplantation in 11/1988 at the age of 34. Hemodialysis was restarted in 02/2006 and hemochromatosis with homozygote C2824 mutation was diagnosed in due course. Biopsy samples of suspicious skin nodules were taken in 12/2005 during a hospitalization for an infected psoas hematoma. The histological analysis of the skin revealed fibrotic dermatitis with calcified blood vessels and nephrogenic systemic fibrosis was subsequently confirmed. In 12/2005, a CT of the head was performed to investigate possible herpes simplex encephalitis (HSE) due to episodes of confusion and impaired consciousness; however, no evidence of HSE was found. Since the CT indicated possible pontine capillary telangiectasia, MRI of the head was performed as well. Pontine capillary telangiectasia was confirmed but the cause of the clinical symptoms could not be determined.

Several kidney MRIs were performed because of progressive renal transplant failure (Table 1). MRI of the head comprised acquisition of unenhanced T1-weighted images on a 1.5 T MR unit (Sonata, Siemens Healthcare, Erlangen, Germany) with the following parameters – time of repetition: 591 msec, time of echo: 13 msec, 1 average. In 2005 the patient's estimated GFR was 30.3 ml/min/m² and her body weight was 80 kg. Thus, the total cumulative GBCA dose before the head MRI was approximately 101 mmol/80 kg = 1.26 mmol/kg. The total cumulative dose of linear GBCAs (considered to be, according to current evidence, associated with gadolinium deposition (8,9)) was 54 mmol/80 kg = 0.68 mmol/kg.

2.2. Patient 2

2.2.1. 61 year-old Caucasian female

Systemic lupus erythematosus was diagnosed in 1986 at the age of 34 and subsequently led to chronic renal failure. Hemodialysis was started in 09/2000 and the patient was kidney transplanted in 06/2005. An MRI performed for connective tissue induration of the thighs revealed no pathologic findings in 10/2005. Further histological workup of the skin showed septal fibrotic panniculitis in 12/2005 and septal fibrosis compatible with NSF in 01/2006.

Table 1. MRI with GBCA received by Patient 1

Date of MRI	Anatomic region	Contrast agent	Administered dose [mmol]
08.1996	Kidneys	Gadodiamide ^a	18
05.2001	Pelvis and kidney transplant	Gadodiamide ^a	16
08.2001	Kidneys	Gadoteridol ^b	16
12.2001	Abdomen	Gadopentetate dimeglumine ^a	10
05.2002	Kidney transplant	Gadoteridol ^b	16
08.2002	Abdomen	Gadopentetate dimeglumine ^a	10
04.2005	Abdomen	Gadoteridol ^b	15
12.2005	Cranium	Gadobutrol ^b	7.5

^aindicates a linear GBCA.
^bindicates a macrocyclic GBCA.

Calcific uremic arteriopathy was diagnosed in 04/2011. In 08/2013 a CT of the head was performed because of a subcutaneous fronto-temporal hematoma caused by a fall. Aphasia and decreased vigilance of the patient were noted. An MRI was performed as well to exclude intracranial hemorrhage. The MRI showed considerable vascular calcifications but no ischemia or bleeding.

A list of the patient's MRIs along with the respective GBCA doses is given in Table 2. MRI of the head comprised acquisition of unenhanced T1-weighted images on a 1.5 T MR unit (Aera, Siemens Healthcare, Erlangen, Germany) with the following parameters – time of repetition: 450 msec, time of echo: 8.4 msec, two averages. In 2013 the patient's estimated GFR was above 60 ml/min/m² and her body weight was 66 kg. Thus, the total cumulative GBCA dose was approximately 53.5 mmol/66 kg = 0.81 mmol/kg. The total cumulative dose of linear GBCAs was 30 mmol/66 kg = 0.45 mmol/kg.

2.3. Patient 3

2.3.1. 65 year-old Caucasian female

Autosomal dominant polycystic kidney disease led to chronic kidney disease necessitating dialysis in 06/1998 at the age of

Table 2. MRI with GBCA received by Patient 2

Date of MRI	Anatomic region	Contrast agent	Administered dose [mmol]
05.2000	Chest	Gadodiamide ^a	15
09.2000	Abdomen	Gadodiamide ^a	15
01.2002	Kidneys	Gadoteridol ^b	16
10.2005	Pelvis and femurs	Gadoterate meglumine ^b	7.5
08.2013	Cranium	/	/

^aindicates a linear GBCA.
^bindicates a macrocyclic GBCA

53. MRI of the abdomen in 08/1999 revealed cysts in the liver and the pancreas. In 12/2003 and 01/2005 MRIs of the head were acquired to investigate reported episodes of loss of strength and consciousness. Supratentorial, primarily subcortical, T2-hyperintense focal lesions due to leukoencephalopathy of likely microangiopathic origin were found. In 03/2006 kidney transplantation was performed. MRI of the liver suggested possible hemosiderosis. Abdominal CT in 10/2006 indicated progressive cyst calcification in the left kidney and the liver. In 11/2009 the patient presented several necrotic skin lesions and calcific uremic arteriopathy was diagnosed. In 03/2010 an MRI of the head was acquired for impaired vigilance and episodes of acute confusional state. The leukoencephalopathy appeared stationary compared with the previous cranial MRI and no additional findings explaining the clinical symptoms were reported.

A list of MRIs with the respective GBCA dose received by Patient 3 is given in Table 3. Unenhanced T1-weighted images were acquired in 2003 and 2005 on a 1.5 T MR unit (Sonata, Siemens Healthcare, Erlangen, Germany) with the following parameters – time of repetition: 591 msec, time of echo: 13 msec, 1 average – and in 2010 on a different 1.5 T MR unit (Avanto, Siemens Healthcare, Erlangen, Germany) with the following parameters – time of repetition: 500 msec, time of echo: 8.4 msec, 1 average. In 2010 the patient's estimated GFR was 46 ml/min/m² and her body weight was 55 kg. Thus, the total cumulative GBCA dose before the last head MRI was approximately 67 mmol/55 kg = 1.22 mmol/kg. If only linear GBCAs are considered, the total cumulative dose was 15 mmol/55 kg = 0.27 mmol/kg.

3. ANALYSIS

The unenhanced T1-weighted images of the three patients presented here revealed conspicuous high signal intensity in the dentate nucleus and the globus pallidus (Figs 1, 2 and 3). Average signal intensities were measured in the dentate nucleus, pons, globus pallidus, and thalamus. Ratios between the signal intensities in the dentate nucleus and the pons (DN-P) and between the signal intensities in the globus pallidus and the thalamus (GP-T) were computed as previously described (14). The results of these quantitative measurements are reported in Tables 4 and 5. The DN-P and GP-T ratios computed for the three patients are of similar magnitude and within the range 1.09 to 1.16.

Table 3. MRI with GBCA received by Patient 3

Date of MRI	Anatomic region	Contrast agent	Administered dose [mmol]
08.1999	Abdomen	Gadodiamide ^a	15
07.2001	Abdomen	Gadoteridol ^b	16
12.2003	Cranium	/	/
04.2004	Abdomen	Gadoteridol ^b	16
09.2004	Abdomen	Gadoteridol ^b	5
01.2005	Cranium	Gadobutrol ^b	5
02.2005	Abdomen	Gadoteridol ^b	5
03.2006	Kidney transplant	Gadoteridol ^b	5
03.2010	Cranium	/	/

^aindicates a linear GBCA.
^bindicates a macrocyclic GBCA.

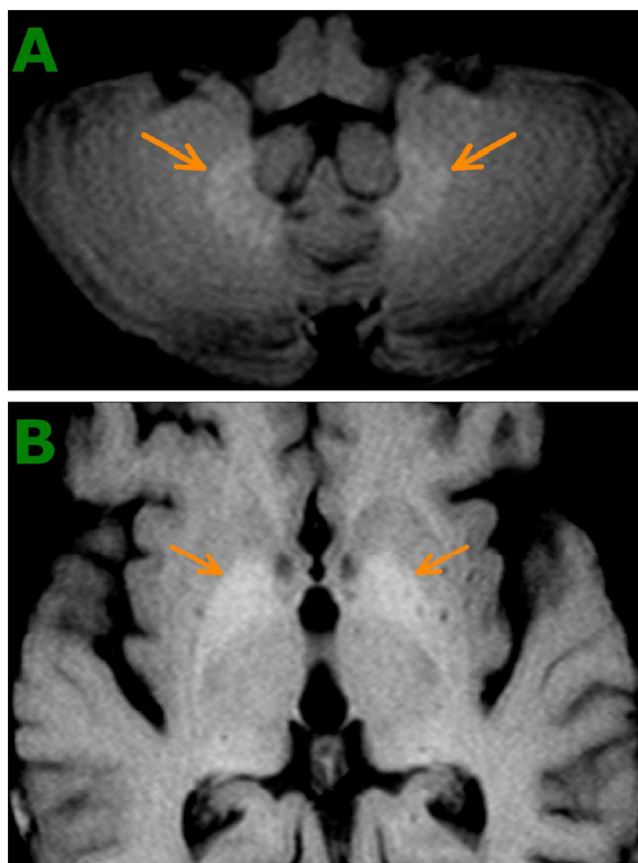


Figure 1. Conspicuous hyperintense dentate nucleus (A) and globus pallidus (B) on T1-weighted MRI of Patient 1.

The DN-P ratio for patient 3 increased from 1.09 in 2003 to 1.13 in 2010. Over the same years, the GP-T ratio for patient 3 remained constant at 1.15.

4. DISCUSSION

Previous studies established that gadolinium deposition occurs in the dentate nucleus and globus pallidus of subjects with normal renal function who were repeatedly exposed to GBCAs with linear chelates (8,9,12–16). The evidence presented here indicates that hyperintensities on unenhanced T1-weighted images can be observed also in patients with renal impairment (e.g. NSF patients).

The cumulative effect of repeated administrations of gadodiamide, a linear GBCA, has been assessed by previous studies on patients with multiple sclerosis or brain metastases (13), or meningioma (19). These studies suggest that a significant increase in DN-P ratios can be detected after six enhanced MRI scans, corresponding to a total cumulative gadodiamide dose of 0.6 mmol/kg. The total doses of linear and macrocyclic GBCAs received by the three patients presented here are above this threshold. However, according to the currently available literature, gadolinium deposits in the brain are associated with linear GBCAs (8,9). Patient 2 in this report received a total of only 0.45 mmol/kg of a linear GBCA (gadodiamide). Patient 3 already presented high DN-P and GP-T ratios in 2003, when she had received only 0.27 mmol/kg of a linear GBCA (gadodiamide) and 0.29 mmol/kg of a macrocyclic GBCA (gadoteridol). This

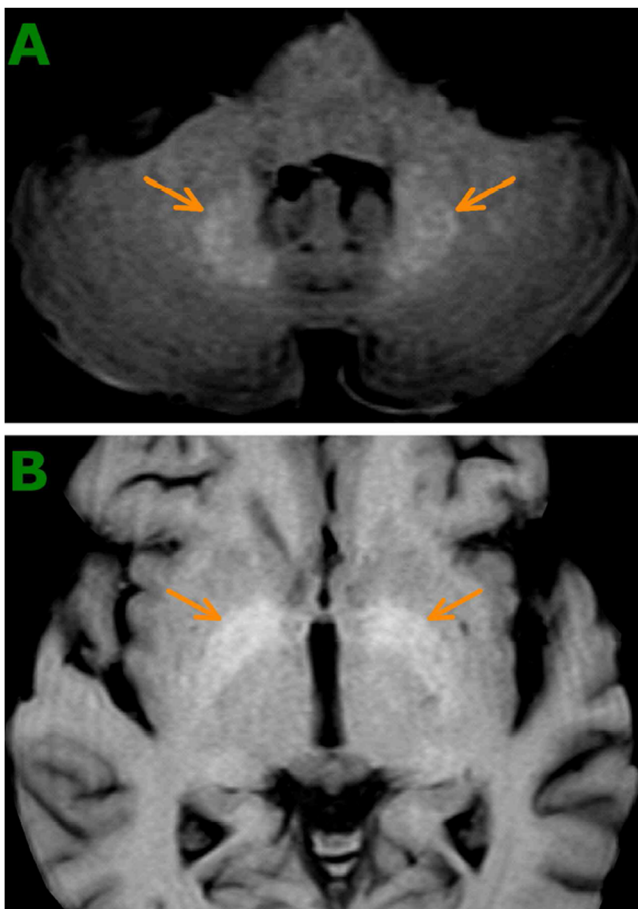


Figure 2. Conspicuous hyperintense dentate nucleus (A) and globus pallidus (B) on T1-weighted MRI of Patient 2.

suggests that reduced renal elimination might lead to increased gadolinium deposition in the brain and to signal hyperintensities on T1-weighted images being detectable at lower cumulative GBCA doses.

Of note, the signal hyperintensity in Patient 2 was visible eight years after her last known exposure to a macrocyclic GBCA and 13 years after her last known exposure to a linear GBCA. Similarly,

Table 4. Average signal intensities (\pm standard deviation) on T1-weighted MRI measured in the various cerebral regions of the three patients

	Patient 1	Patient 2	Patient 3 (2003)	Patient 3 (2005)	Patient 3 (2010)
Dentate nucleus	430 \pm 6	242 \pm 4	420 \pm 6	463 \pm 8	503 \pm 7
Pons	371 \pm 5	215 \pm 4	385 \pm 6	417 \pm 7	445 \pm 9
Globus pallidus	409 \pm 5	250 \pm 3	420 \pm 7	462 \pm 6	515 \pm 9
Thalamus	368 \pm 5	219 \pm 3	365 \pm 6	402 \pm 7	447 \pm 8

Table 5. Ratios of dentate nucleus to pons and globus pallidus to thalamus signal intensities measured in the three patients

	Patient 1	Patient 2	Patient 3 (2003)	Patient 3 (2005)	Patient 3 (2010)
DN-P ratio	1.16	1.13	1.09	1.11	1.13
GP-T ratio	1.11	1.14	1.15	1.15	1.15

signal hyperintensity in Patient 3 was visible 11 years after her last known exposure to a linear GBCA. This long-lasting visibility of gadolinium accumulation is in line with studies reporting that gadolinium deposits in bones can be observed many years after exposure to GBCA (20–22). It has even been suggested that bones might act as a reservoir for successive long-term release of gadolinium into the bloodstream (20).

The DN-P and GP-T ratios computed here in patients with renal impairment are compatible with the results of previous studies analysing the cumulative effect of multiple administrations of linear GBCAs in subjects with normal renal function (12,14). It might be hypothesized that after several enhanced MRI scans the amount of gadolinium deposition in the brain does not differ significantly between patients with and without impaired renal function. The computed ratios are also of similar magnitude in the three analysed patients despite considerable

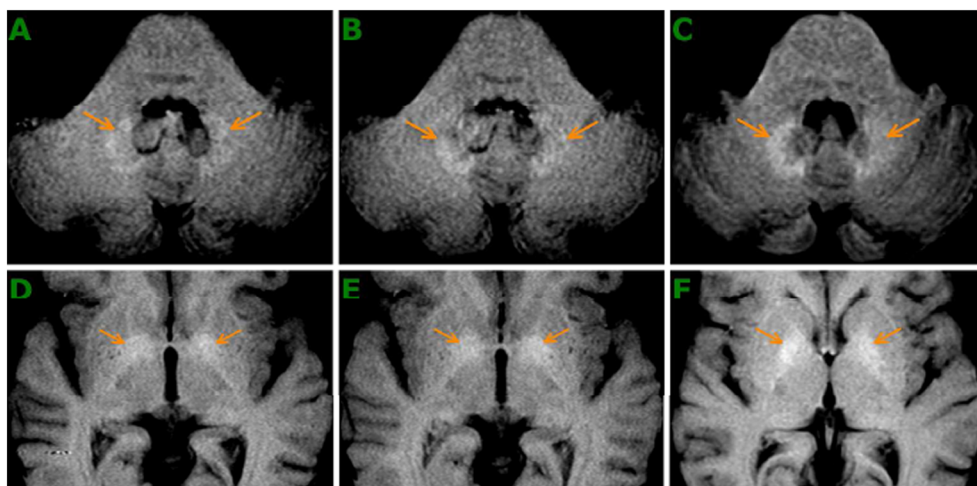


Figure 3. Conspicuous hyperintense dentate nucleus (A: 2003, B: 2005, C: 2010) and globus pallidus (D: 2003, E: 2005, F: 2010) on T1-weighted MRI of Patient 3.

differences in the cumulative amount of GBCA. This suggests saturation of the dentate nucleus and globus pallidus with gadolinium and that higher order models (12) might be better suited to describe the accumulation process than linear ones (13,14). A trend of increasing DN-P ratios and constant GP-T ratios was observed over the years in patient 3; this could indicate that saturation in the globus pallidus occurs earlier than in the dentate nucleus.

It is currently unclear whether gadolinium accumulates in neural tissue in the form of chelates, as dissociated ions, or both. Additional investigations are also needed to clarify the mechanism by which gadolinium crosses the blood-brain barrier. It has been suggested that gadolinium deposits are associated with vascular calcifications (17). In addition, it is possible that calcification contributes to the pathophysiology of NSF (18) or that pre-existing calcium deposits might facilitate the release of toxic gadolinium ions (suggesting transmetallation or transchelation) and predispose to the development of NSF (23). Gadolinium itself might contribute to the formation of insoluble calcium- and gadolinium-phosphates and to the pro-fibrotic action of macrophages (24).

NSF presents clear signs of foreign body toxicology such as activation of the unspecific immune system, inflammation resulting in fibrosis, and progressive deterioration of connecting tissue. Therefore, further research on NSF's pathomechanism and on the histopathological changes that occur in the dentate nucleus and the globus pallidus might be useful to investigate the potential neurotoxic consequences of gadolinium deposits in specific parts of the brain (25).

The deposition of manganese (26,27) or copper (28) in the dentate nucleus correlates with neurobehavioral deficits. As both the dentate nucleus and the globus pallidus play a central role in regulating and controlling voluntary movement, the deposition of gadolinium in these areas might lead to similar deficits. Of note, all three analysed patients suffered from transient signs of neurological disorders of undetermined cause. However, the functional significance of our findings is currently not clear.

As the patients analysed in this report were exposed to different GBCAs, specific inferences about single compounds (or even about linear or macrocyclic GBCAs) cannot be made. In addition, it cannot be excluded that vascular calcification or minerals supplemented during dialysis were additional causes for the observed signal hyperintensities (29,30).

5. CONCLUSION

Signal hyperintensity within the dentate nucleus and the globus pallidus on unenhanced T1-weighted MR images, likely corresponding to gadolinium deposits, was observed in three patients (two with NSF) following exposure to relatively low doses of linear GBCAs (0.27, 0.45, and 0.68 mmol/kg body weight). Impaired renal function and vascular calcification (including calcific uremic arteriopathy) might be factors contributing to increased gadolinium deposition. GBCAs should be administered with particular caution to this group of patients. Additional research is needed to determine the possible clinical consequences of gadolinium deposits in the brain.

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