



Original contribution

Diffusion-weighted imaging of the dentate nucleus after repeated application of gadolinium-based contrast agents in multiple sclerosis

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ABSTRACT

Objective: Over the last years several studies reported an increased signal intensity (SI) of the dentate nucleus (DN) on unenhanced T1-weighted images after repeated application of gadolinium-based contrast agents (GBCAs), suggesting gadolinium deposition. The aim of this study was to investigate with diffusion-weighted MRI possible tissue abnormalities of the DN in multiple sclerosis (MS) patients.

Material and methods: We retrospectively identified seventeen patients with at least six contrast-enhanced MRI examinations by using the linear GBCA gadopentate dimeglumine and twenty-three patients with the exclusive use of the macrocyclic contrast agent gadoterate meglumine followed by another 3 Tesla MRI scan including unenhanced T1-weighted and diffusion-weighted images.

Results: In the linear GBCA group, we found significant differences of the DN-to-pons SI ratio on unenhanced T1-weighted images (1.13 ± 0.05) when compared to the macrocyclic GBCA group (0.97 ± 0.03 ; $p < 0.001$). However, we found no significant differences between apparent diffusion coefficient (ADC) values of the DN in both groups (linear GBCA group: $0.82 \pm 0.04 \times 10^{-3} \text{ mm}^2/\text{s}$; macrocyclic GBCA group: $0.79 \pm 0.04 \times 10^{-3} \text{ mm}^2/\text{s}$; $p = 0.15$).

Conclusions: Our results do not suggest that there is any difference in ADC values in the T1-hyperintense DN, which does not indicate a difference in tissue integrity between patients exposed to macrocyclic or linear GBCAs.

1. Introduction

Multiple sclerosis (MS) is a chronic, autoimmune, inflammatory-demyelinating and neurodegenerative disease of the central nervous system. With more than two million people affected worldwide, MS represents the leading cause of non-traumatic irreversible substantial neurological disability in young adults [1]. Conventional magnetic resonance imaging (MRI) supports and substitutes clinical information and represents the most sensitive paraclinical biomarker enabling early diagnosis, disease monitoring and treatment decisions [2].

Following the initial study by Kanda et al. [3], several studies reported an association between an increasing signal intensity (SI) of the dentate nucleus (DN) on unenhanced T1-weighted images and repeated

application of some gadolinium-based contrast agents (GBCAs) [4–7] and autopsy studies verified the accumulation of gadolinium in brain areas including the DN [8–11]. Subsequently, two retrospective studies by Radbruch et al. [12] and Kanda et al. [13] reported that T1 hyperintensity of the DN is associated with the previous administration of linear GBCAs, but not with the administration of macrocyclic GBCAs, that has been subsequently confirmed by clinical [14–16] and experimental studies [17–19].

The discussion of an abnormal gadolinium deposition is particularly relevant in patients with MS in whom repeated MRI is performed and it must be assumed that MS patients might theoretically pose a higher risk for gadolinium deposition in the brain. Over the last years, various studies focused on the relationship between an increased SI on

Abbreviations: ADC, apparent diffusion coefficient; GBCA, gadolinium-based contrast agent; DN, dentate nucleus; EDSS, Expanded Disability Status Scale; FLAIR, fluid-attenuated inversion recovery; MPRAGE, magnetization-prepared rapid acquisition gradient-echo; MRI, magnetic resonance imaging; MS, multiple sclerosis; ROI, region of interest; SI, signal intensity

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unenanced T1-weighted images and exposure to intravenously injected GBCAs in MS patients [14–16,20–24]. However, conventional MRI sequences lack of specific histopathological information and can therefore only provide a small window into the underlying pathophysiological processes. The aim of this study was to investigate abnormal tissue integrity of the DN using diffusion-weighted MRI in patients with MS.

2. Materials and methods

The local ethics committee approved this study. Patient consent was not required due to the retrospective nature of the study and the lack of patient interaction.

2.1. Patients

We retrospectively screened our database to identify two groups of patients with MS who met the following inclusion criteria: (a) diagnosis of relapsing-remitting MS [25], (b) MRI follow-up performed exclusively in our department, (c) at least six contrast-enhanced MRI examinations with the use of the linear GBCA gadopentate dimeglumine (linear GBCA group) or with the exclusive use of the macrocyclic contrast agent gadoterate meglumine (macrocyclic GBCA group) followed by another 3 Tesla MRI scan including unenanced T1-weighted and diffusion-weighted images and (d) no history of more than two contrast-enhanced MRI examinations with different or unknown GBCA as proposed previously [26]. Therefore, medical records were analyzed for the frequency of prior MR imaging outside of our department. In October 2007, our department switched from gadopentate dimeglumine to gadoterate meglumine as the predominant contrast-agent, therefore MS patients first receiving the linear GBCA might have been investigated with the macrocyclic contrast-agent after October 2007. In these cases, the earliest MRI examination including unenanced T1- and diffusion-weighted images after the change of the contrast-agent was used for image analysis. A schematic description of the study design is presented in Fig. 1. Exclusion criteria were (a) estimated glomerular filtration rate < 60 ml/min, (b) abnormal serum concentrations of aspartate aminotransferase, alanine aminotransferase, total bilirubin or γ -glutamyl transpeptidase, (c) missing data or unsatisfactory image quality of unenanced T1- and/or diffusion-weighted images, (d) lesions located in the DN, cerebellum or pons causing difficulties for accurate placement of regions-of-interest (ROIs) and (e) current or past radiation or chemotherapy.

2.2. Magnetic resonance imaging protocol

MRI examinations used for image analysis were performed on a 3.0 T MR system (MAGNETOM Skyra, Siemens, Germany). The standard MR imaging protocol included (1) diffusion-weighted echo planar [EP] images (TR 5300 ms / TE 68 ms / b = 0/500/1000 s/mm², field-of-view

220 × 220 mm², slice thickness 4 mm), including apparent diffusion coefficient (ADC) calculations (calculated on a pixel-by-pixel basis by a linear least-squares fit after averaging of the direction-dependent DW images), (2) a high resolution 3D magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequence (TE = 2.49 ms, TR = 1900 ms, TI = 900 ms, field-of-view 240 × 240 mm², spatial resolution = 0.9 × 0.9 × 0.9 mm³) and (3) a 3D fluid-attenuated inversion recovery (FLAIR)-data set (TE = 398 ms, TR = 5000 ms, TI = 1800 ms, field-of-view 240 × 240 mm², resolution = 0.5 × 0.5 × 0.9 mm³).

2.3. Data processing and analysis

2.3.1. Signal intensity analysis on unenanced T1-weighted images

Image analysis was performed offline by an experienced blinded reader on our picture archiving and communication system as proposed previously by Radbruch et al. [12]: Oval ROIs were placed on the unenanced T1-weighted images on the central pons and around the left and right DN. In cases the DN was not clearly visible on unenanced T1-weighted images, FLAIR images were used to guide ROI placement. To obtain the DN-to-pons SI ratio, the mean SI of the right and left DN was divided by the mean SI of the central pons.

2.3.2. ADC calculations

The DN is relatively small and not always easy to delineate on ADC maps, posing challenges for quantitative analysis. To facilitate analysis of ADC calculations, ADC maps were co-registered onto the FLAIR images using the automated FLIRT tool, part of FSL (version 5.0.2.1; <http://fsl.fmrib.ox.ac.uk/fsl/>). A second independent reader blinded to clinical data and information of the unenanced T1-weighted images identified the DN on FLAIR images with a semi-automated assistance with the drawing tool of MRICron (<http://www.mccauslandcenter.sc.edu/mricron/mricron/>). The resulting masks were applied to the quantitative ADC maps, mean ADC values were extracted offline on a workstation for each subject and used for statistical assessment.

2.4. Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics Version 22. Group comparisons of demographic variables across the study groups were analyzed using a chi-square-test (i.e. gender). A paired *t*-test was used to compare the DN-to-pons SI ratio on unenanced T1-weighted images as well as ADC values of the DN between the two groups. Correlations between the DN-to-pons SI ratio, disease duration, number of MRI examinations and age were assessed using Pearson's correlation coefficient. Since the EDSS is not normally distributed, correlations between age, disease duration, number of contrast-enhanced MRI examinations, DN-to-pons SI ratio on unenanced T1-weighted images and ADC values of the DN and EDSS were assessed using Spearman's rank correlation coefficient.

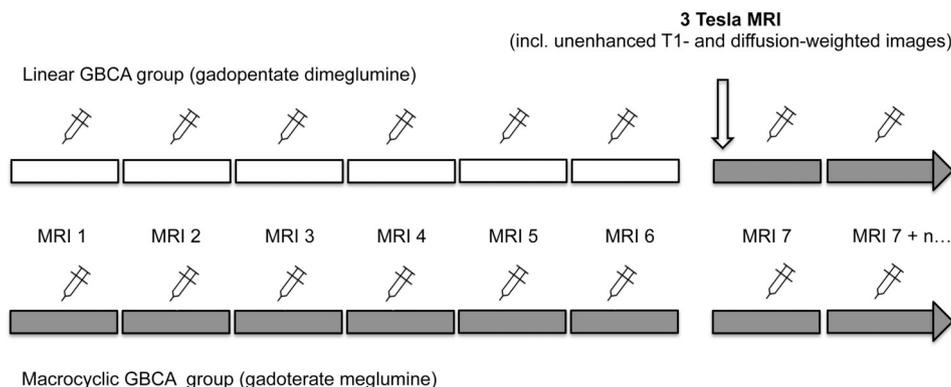


Fig. 1. Schematic of the study design. In 2007, our department switched from the linear gadolinium-based contrast agent (GBCA) gadopentate dimeglumine to the macrocyclic GBCA gadoterate meglumine as the predominant contrast-agent and therefore patients first receiving the linear GBCA might have been investigated with the macrocyclic contrast-agent after 2007.

Table 1
Patient characteristics and radiologic data.

	Linear GBCA group	Macrocytic GBCA group	p Value
Total no. of subjects	17	23	–
Age (years), mean ± SD	42.4 ± 8.6	35.8 ± 9.4	0.02
Female sex (%)	76	82	0.7
Mean disease duration, years (range)	13.7 (3–26)	5.4 (2–10)	< 0.001
Median EDSS (range)	3.5 (1–8)	1.5 (0–6)	0.003
Mean no. of MRI examinations ± SD	15 ± 8	6 ± 2	< 0.001
Disease modifying therapy (%)	82	91	0.63

Abbreviations: EDSS = Expanded Disability Status Scale; GBCA = Gadolinium-based contrast agent; SD = standard deviation.

3. Results

Patient characteristics of the study population and radiological data according to the type of GBCAs are presented in Table 1. A total of 40 MS patients were included in the study. Seventeen patients received at least six times the linear GBCA gadopentate dimeglumine, twenty-three patients at least six contrast-enhanced MRI examinations by using exclusively the macrocytic contrast agent gadoterate meglumine. Both groups were comparable regarding sex and disease-modifying therapies, whereas age, disease duration and Expanded disability status scale (EDSS) score differed statistically significant between the two groups.

In the linear GBCA group, we found significant differences of the DN-to-pons SI ratio on unenhanced T1-weighted images (1.13 ± 0.05) when compared to the macrocytic GBCA group (0.97 ± 0.03 ; $p < 0.001$; see also Table 2). However, we found no significant differences between ADC values of the DN in both groups (linear GBCA group: $0.82 \pm 0.04 \times 10^{-3} \text{ mm/s}^2$; macrocytic GBCA group: $0.79 \pm 0.04 \times 10^{-3} \text{ mm/s}^2$; $p = 0.15$). ADC values of the DN only showed a modest correlation between the DN-to-pons SI ratio on unenhanced T1-weighted images ($p = 0.023$). Disease duration and number of contrast-enhanced MRI examinations showed a strong correlation with the DN-to-pons SI ratio on unenhanced T1-weighted images ($p < 0.001$ for both comparisons), but not with ADC values of the DN ($p = 0.33$ and 0.2). There was no correlation between EDSS and ADC values of the DN ($p = 0.83$) and the DN-to-pons SI ratio on unenhanced T1-weighted images ($p = 0.06$). Furthermore, we observed no correlation between age and ADC values of the DN, or between age and the DN-to-pons SI ratio on unenhanced T1-weighted images ($p > 0.05$ for all comparisons).

Fig. 2 demonstrates representative examples of a MS patient with an increased signal intensity of the DN on unenhanced T1-weighted images and a MS patient without those signal abnormalities. On ADC maps no different ADC values are observed. Fig. 3 shows a scatterplot of the correlation between the DN-to-pons SI ratio on unenhanced T1-weighted images and ADC values.

4. Discussion

In this study we investigated signal abnormalities of the DN on diffusion-weighted MRI in patients with MS after multiple applications

Table 2
Results.

	Linear GBCA group	Macrocytic GBCA group	p value
DN-to-Pons ratio (unenhanced T1) ± SD	1.13 ± 0.5	0.97 ± 0.03	< 0.001
ADC DN ($\times 10^{-3} \text{ mm/s}^2$) ± SD	0.82 ± 0.04	0.79 ± 0.04	0.155

Abbreviations: ADC = apparent diffusion coefficient; DN = dentate nucleus; GBCA = Gadolinium-based contrast agent; SD = standard deviation.

of GBCAs. While most recent studies evaluated gadolinium deposition on unenhanced T1-weighted images, only a few studies investigated signal abnormalities of the DN on advanced MRI techniques [21,27,28].

Diffusion-weighted MRI investigates water mobility that occurs as part of the physical diffusion process in the brain and in contrast to conventional MRI techniques represents a sensitive quantitative marker of microstructural tissue damage. Alterations in the apparent water diffusion rate reflect pathological changes in the brain tissue state via changes in the diffusion characteristics of the intra- and extracellular water compartments including restricted diffusion, water exchange across permeable boundaries, the concept of the extracellular tortuosity and the intra- and extracellular volume fraction [29]. A reduction of the ADC has been detected in different acute neurological diseases accompanied by cytotoxic cell swelling such as stroke [30], non-convulsive status epilepticus [31] and acute MS lesions in the absence of contrast-enhancement [32–35], while disease states associated with dominant vasogenic edema formation or chronic tissue destruction regularly show elevations of the ADC. In MS, several studies demonstrated that diffusion-weighted MRI is sensitive in detecting tissue changes in focal lesions [32,33] and the normal-appearing brain tissue [33,36,37]. The ADC increase is more pronounced in T1-hypointense lesions and higher than in the normal-appearing white matter [33] confirming that diffusion-weighted MRI is a sensitive marker of tissue damage. Recently, a post-mortem study demonstrated that after intravenous exposure a considerable amount of gadolinium had crossed the intact blood-brain-barrier and deposited into the neural tissue interstitium [8]. One might have assumed that gadolinium deposition could result in signal alterations on diffusion-weighted MRI as a result of tissue damage, but our results argue the convers. Instead, our results endorse the findings of an experimental study comparing linear and macrocytic GBCAs that demonstrated no tissue changes in areas of Gadolinium deposition [18].

This study is not without limitations: Our study was a retrospective, cross-sectional analysis and the sample size was relatively small. Furthermore, due to the small size of the DN quantitative MRI studies remain challenging. Even though ADC maps were co-registered onto the 3D-FLAIR images to facilitate analysis, images were acquired using different spatial resolutions. Therefore, interpretation of the results needs to be done cautiously. Higher field strengths and further technical improvement could permit better spatial resolution and better quantitative measurements of ADC values in the future. Investigation of differences of axial and radial diffusivity as diffusion tensor imaging markers of axonal and myelin integrity and damage between the linear GBCA and macrocytic GBCA groups would also be of interest. As in most of the published retrospective studies, we cannot definitely exclude previous injections of GBCAs prior to the first analyzed images in our department. Although we analyzed medical records for the frequency of prior MR imaging outside of our department and excluded patients with a history of more than two contrast-enhanced MRI examinations with different or unknown GBCA as proposed by Radbruch et al. [26], it is likely that some of the included patients received previous injections of unknown GBCAs. Additionally, our department switched from gadopentate dimeglumine to gadoterate meglumine as the predominant contrast-agent in 2007 and therefore patients first receiving the linear GBCA might have been investigated with the macrocytic contrast-agent thereafter. Radbruch and colleagues reported that pre-existing T1 hyperintensity of the DN due to repeated application of linear GBCAs might slightly decrease over time after changing to a macrocytic GBCA [38]. As a consequence, the DN-to-pons SI ratio in our linear GBCA group might have been underestimated due to a “wash-out” effect or a precipitation of gadolinium that would reduce the T1-shortening in the affected areas. Finally it is important to point out that we cannot exclude any changes on ADC maps if > 6 injections of GBCAs are applied.

5. Conclusion

In conclusion, our data does not suggest that there is any difference in ADC values in the T1-hyperintense DN, which does not indicate a

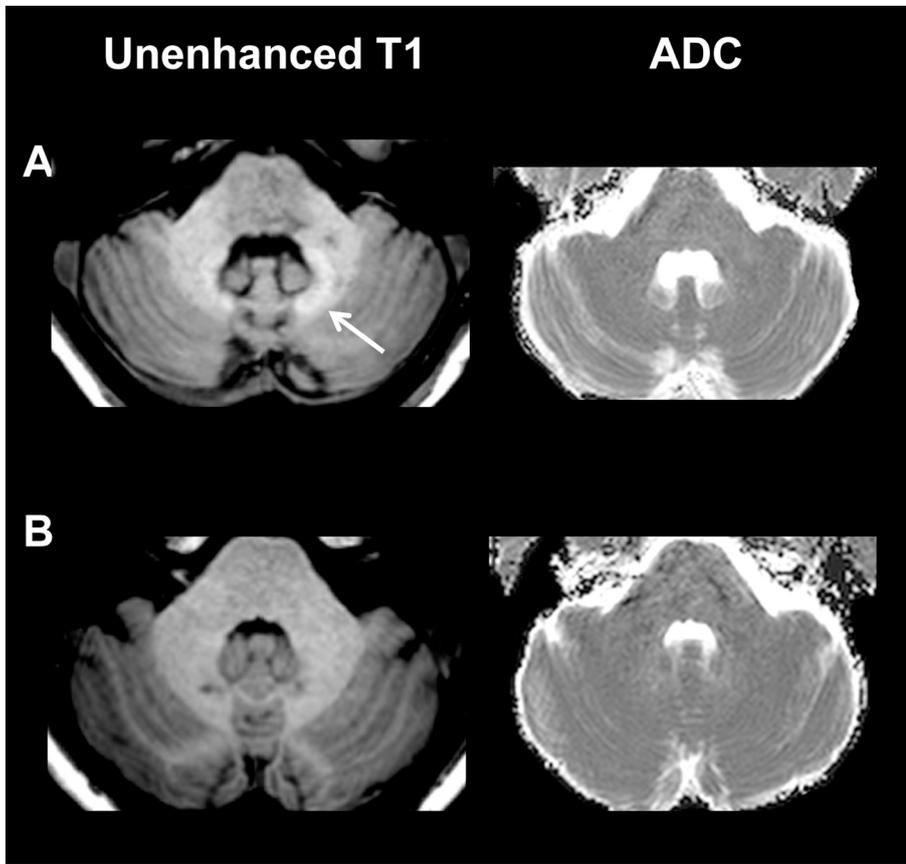


Fig. 2. Exemplary unenhanced T1-weighted images (left) and apparent diffusion coefficient (ADC) maps at the level of the dentate nucleus in a multiple sclerosis patient demonstrating an increased signal intensity of the dentate nucleus (A, arrow) and a patient without signal abnormalities of the dentate nucleus (B). On ADC maps, no significant differences in both patients are detectable.

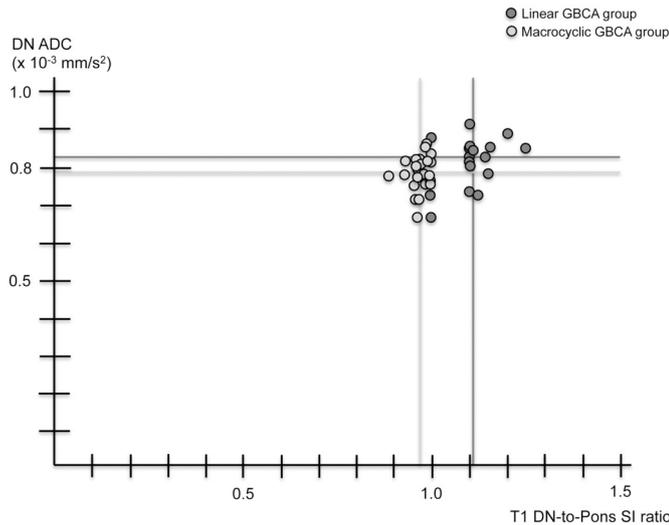


Fig. 3. Scatterplot of the DN-to-pons SI ratio on unenhanced T1-weighted images and ADC values. Vertical and horizontal lines indicate mean values of the DN-to-pons SI ratio on unenhanced T1- images, as well as ADC values of the DN. No significant differences of ADC values between the linear and macrocytic GBCA groups are detectable.

difference in tissue integrity between patients exposed to macrocytic or linear GBCAs.

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Conflict of interests

Dr. Eisele has received travel expenses from Bayer Health Care. Prof. Szabo has received research support from the German Research Foundation (DFG). Dr. Ebert reports no disclosures. Prof. Radbruch has received personal fees for talks and advisory boards from Abbvie, Bayer, Bracco, GE and Guerbet, Siemens and study support from Bayer and Guerbet. Prof. Platten has a consultant relationship with Novartis, Merck, Genentech/Roche, Affiris, has received non-personal, institutional honoraria from Medac, Merck, Novartis, Teva, Genentech/Roche and has research agreements with Bayer Health Care. Prof. Schoenberg reports that the institute of clinical radiology and nuclear medicine has research agreements with Siemens Healthineers GmbH. Prof. Gass has received honoraria for speaking engagements and attendance at advisory boards, and financial support for research from Bayer, Biogen, Merck Serono, Novartis, Sanofi, Celgene, Roche.

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