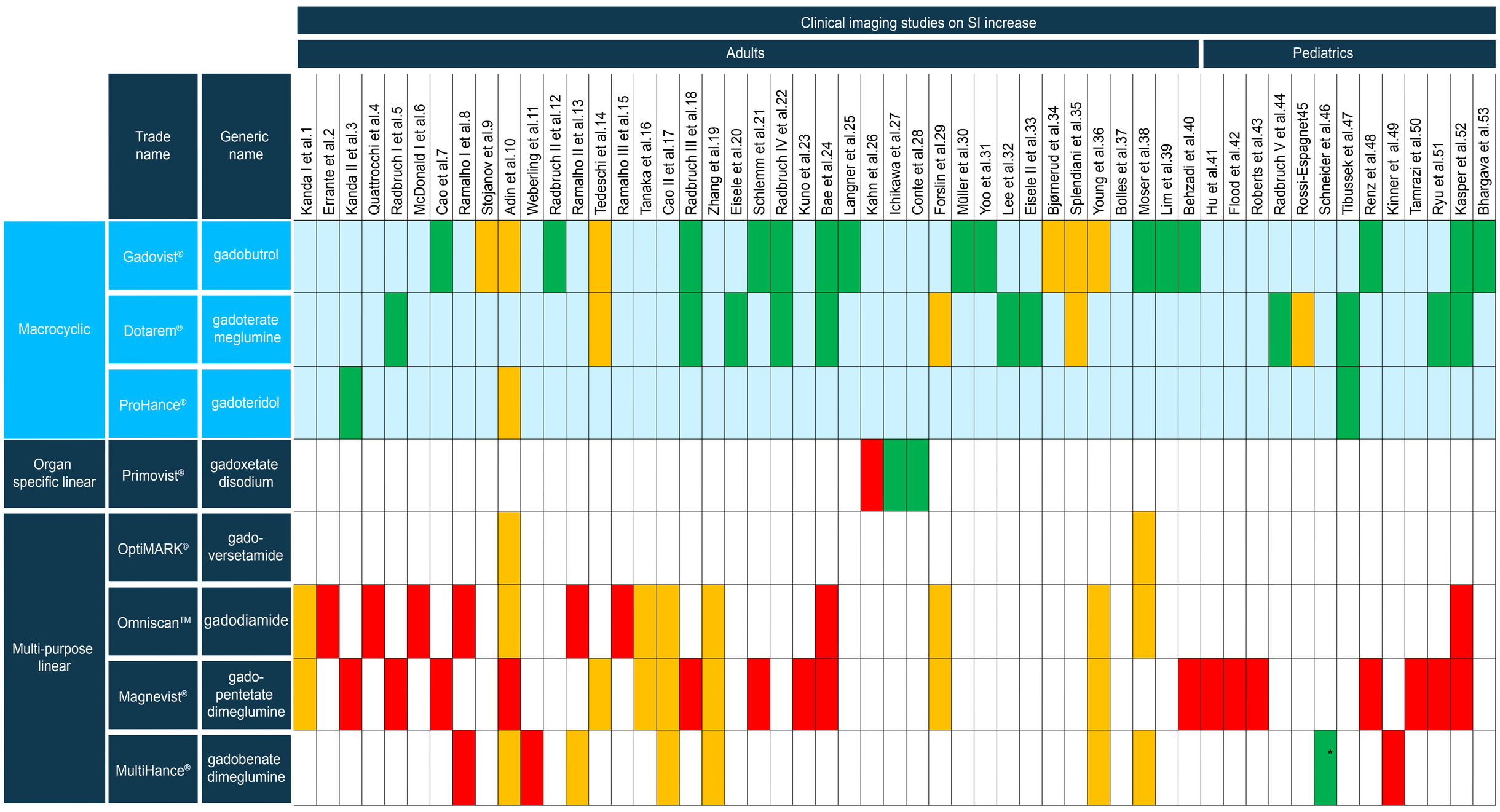
Table 1. Summary of key findings of clinical imaging studies that try to associate various gadolinium based contrast agents with signal intensity increase in the brain.



* Schneider and colleagues administered MultiHance at a dose of 0.05 mmol/kg which is a calculated mean dose of 3.9. A certain threshold in terms of dose/numbers of injections has to be reached in order to see an effect on SI increase. No individual baseline to follow-up comparisons provided on a patient level. Results are presented as statistical mean for the entire study cohort. Hyperintensity in the DN and GP brain areas has been observed after 5 or more administrations of multi-purpose linear GBCAs (Omniscan, MultiHance and Magnevist) with standard dose (0.1 mmol/kg bw). Pediatric studies 41, 43, 47, 48, 51, 54, 55 with standard dose (0.1 mmol/kg/bw) of multi-purpose linear GBCAs administered had similar results as in adults. 1-5, 8, 11, 21, 23, 24

- The authors concluded that no association of repeated administration of the respective gadolinium based contrast agent (GBCA) with a SI increase in the brain exists
- A visual and statistically significant measureable SI increase in the brain was reported in the publication and the respective GBCA was clearly assigned by the authors
- The assignment of a single GBCA is either unknown or the data are suggestive of other potential confounding factors, e.g.
  - Administration of multiple/different GBCAs to one patient or a patient cohort documented by the author of the publication
  - Potential confounding factors and limitations acknowledged by the authors of the publication
  - Strong doubts with regard to validity of the study were expressed by independent experts
  - Implausible increased SI ratio was measured between first and last scan, however no increased SI visualized on MR scan
  - The quantitative analysis and image interpretation are not robust/plausible because of: Potential for previous administrations of other GBCAs or difference in the MR scan slices as well as non-comparative image windowing between baseline and last exam, or non-standardized ROI measurement or inappropriate statistics

1. Kanda T, Ishii K, Kawaguchi H, Kitajima K, Takenaka D. 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. Radiology 2014;270:834-41
2. Errante Y, Cirimele V, Mallio CA, Di Lazzaro V, Zobel BB, Quattrocchi CC. Progressive increase of T1 signal intensity of the dentate nucleus on unenhanced magnetic resonance images is associated with cumulative doses of intravenously administered gadodiamide in patients with normal renal function, suggesting dechelation. Investigative radiology 2014;49:685-90
3. Kanda T, Osawa M, Oba H, et al. High Signal Intensity in Dentate Nucleus on Unenhanced T1-weighted MR Images: Association with Linear versus Macrocyclic Gadolinium Chelate Administration. Radiology 2015;275:803-9
4. Quattrocchi CC, Mallio CA, Errante Y, et al. Gadodiamide and Dentate Nucleus T1 Hyperintensity in Patients With Meningioma Evaluated by Multiple Follow-Up Contrast-Enhanced Magnetic Resonance Examinations With No Systemic Interval Therapy. Investigative radiology 2015;50:470-2
5. Radbruch A, Weberling LD, Kieslich PJ, et al. Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. Radiology 2015;275:783-91.
6. McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial Gadolinium Deposition after Contrast-enhanced MR Imaging. Radiology 2015;275:772-82
7. Cao Y, Huang DQ, Shih G, Prince MR. Signal Change in the Dentate Nucleus on T1-Weighted MR Images After Multiple Administrations of Gadopentetate Dimeglumine Versus Gadobutrol. AJR American journal of roentgenology 2016;206:414-9
8. Ramalho J, Castillo M, AlObaidy M, et al. High Signal Intensity in Globus Pallidus and Dentate Nucleus on Unenhanced T1-weighted MR Images: Evaluation of Two Linear Gadolinium-based Contrast Agents. Radiology 2015;276:836-44
9. Stojanov DA, Aracki-Trenkic A, Vojinovic S, Benedeto-Stojanov D, Ljubisavljevic S. Increasing signal intensity within the dentate nucleus and globus pallidus on unenhanced T1W magnetic resonance images in patients with relapsing-remitting multiple sclerosis: correlation with cumulative dose of a macrocyclic gadolinium-based contrast agent, gadobutrol. European radiology 2016;26:807-15
10. Adin ME, Kleinberg L, Vaidya D, Zan E, Mirbagheri S, Yousem DM. Hyperintense Dentate Nuclei on T1-Weighted MRI: Relation to Repeat Gadolinium Administration. AJNR American journal of neuroradiology 2015;36:1859-65
11. Weberling LD, Kieslich PJ, Kickingereder P, et al. Increased Signal Intensity in the Dentate Nucleus on Unenhanced T1-Weighted Images After Gadobenate Dimeglumine Administration. Investigative radiology 2015;50:743-8
12. Radbruch A, Weberling LD, Kieslich PJ, et al. High-Signal Intensity in the Dentate Nucleus and Globus Pallidus on Unenhanced T1-Weighted Images: Evaluation of the Macrocyclic Gadolinium-Based Contrast Agent Gadobutrol. Investigative radiology 2015;50:805-10
13. Ramalho J, Ramalho M, AlObaidy M, Nunes RH, Castillo M, Semelka RC. T1 Signal-Intensity Increase in the Dentate Nucleus after Multiple Exposures to Gadodiamide: Intraindividual Comparison between 2 Commonly Used Sequences. AJNR American journal of neuroradiology 2016
14. Tedeschi E, Palma G, Canna A, et al. In vivo dentate nucleus MRI relaxometry correlates with previous administration of Gadolinium-based contrast agents. European radiology 2016;26:4577-84
15. Ramalho J, Ramalho M, AlObaidy M, Semelka RC. Technical aspects of MRI signal change quantification after gadolinium-based contrast agents' administration. Magn Reson Imaging 2016;34:1355-8
16. Tanaka M, Nakahara K, Kinoshita M. Increased Signal Intensity in the Dentate Nucleus of Patients with Multiple Sclerosis in Comparison with Neuromyelitis Optica Spectrum Disorder after Multiple Doses of Gadolinium Contrast. Eur Neurol 2016;75:195-8
17. Cao Y, Zhang Y, Shih G, et al. Effect of Renal Function on Gadolinium-Related Signal Increases on Unenhanced T1-Weighted Brain Magnetic Resonance Imaging. Investigative radiology 2016;51:677-82
18. Radbruch A, Weberling LD, Kieslich PJ, et al. Intraindividual Analysis of Signal Intensity Changes in the Dentate Nucleus After Consecutive Serial Applications of Linear and Macrocyclic Gadolinium-Based Contrast Agents. Investigative radiology 2016;51:683-90
19. Zhang Y, Cao Y, Shih GL, Hecht EM, Prince MR. Extent of Signal Hyperintensity on Unenhanced T1-weighted Brain MR Images after More than 35 Administrations of Linear Gadolinium-based Contrast Agents. Radiology 2016:152864
20. Eisele P, Alonso A, Szabo K, et al. Lack of increased signal intensity in the dentate nucleus after repeated administration of a macrocyclic contrast agent in multiple sclerosis: An observational study. Medicine (Baltimore) 2016;95:e462
21. Schlemm L, Chien C, Bellmann-Strobl J, et al. Gadopentetate but not gadobutrol accumulates in the dentate nucleus of multiple sclerosis patients. Mult Scler 2016.
22. Radbruch A, Haase R, Kieslich PJ, et al. No Signal Intensity Increase in the Dentate Nucleus on Unenhanced T1-weighted MR Images after More than 20 Serial Injectios of Macrocyclic Gadolinium-based Contrast Agents. Radiology 2016:162241
23. Kuno H, Jara H, Buch K, Qureshi MM, Chapman MN, Sakai O. Global and Regional Brain Assessment with Quantitative MR Imaging in Patients with Prior Exposure to Linear Gadolinium-based Contrast Agents. Radiology 2017;283:195-204
24. Bae S, Lee HJ, Han K, et al. Gadolinium deposition in the brain: association with various GBCAs using a generalized additive model. European radiology 2017
25. Langner S, Kromrey ML, Kuehn JP, Grothe M, Domin M. Repeated intravenous administration of gadobutrol does not lead to increased signal intensity on unenhanced T1-weighted images-a voxel-based whole brain analysis. European radiology 2017
26. Kahn J, Posch H, Steffen IG, et al. Is There Long-term Signal Intensity Increase in the Central Nervous System on T1-weighted Images after MR Imaging with the Hepatospecific Contrast Agent Gadoxetic Acid? A Cross-sectional Study in 91 Patients. Radiology 2017:162535
27. Ichikawa S, Motosugi U, Omiya Y, Onishi H. Contrast Agent-Induced High Signal Intensity in Dentate Nucleus on Unenhanced T1-Weighted Images: Comparison of Gadodiamide and Gadoxetic Acid. Investigative radiology 2017
28. Conte G, Preda L, Cocorocchio E, et al. Signal intensity change on unenhanced T1-weighted images in dentate nucleus and globus pallidus after multiple administrations of gadoxetate disodium: an intraindividual comparative study. European radiology 2017
29. Forslin Y, Shams S, Hashim F, et al. Retention of Gadolinium-Based Contrast Agents in Multiple Sclerosis: Retrospective Analysis of an 18-Year Longitudinal Study. AJNR American journal of neuroradiology 2017
30. Muller A, Jurcoane A, Madler B, Ditter P, Schild H, Hattingen E. Brain relaxometry after macrocyclic Gd-based contrast agent. Clin Neuroradiol 2017
31. Yoo RE, Sohn CH, Kang KM, et al. Evaluation of Gadolinium Retention After Serial Administrations of a Macrocyclic Gadolinium-Based Contrast Agent (Gadobutrol): A Single-Institution Experience With 189 Patients. Investigative radiology 2017
32. Lee JY, Park JE, Kim HS, et al. Up to 52 administrations of macrocyclic ionic MR contrast agent are not associated with intracranial gadolinium deposition: Multifactorial analysis in 385 patients. PLoS One 2017;12:e0183916
33. Eisele P, Szabo K, Alonso A, et al. Lack of T1 hyperintensity in the dentate nucleus after 15 administrations of a macrocyclic contrast agent in multiple sclerosis. J Neurol Neurosurg Psychiatry 2017
34. Bjornerud A, Vatnehol SAS, Larsson C, Due-Tonnessen P, Hol PK, Groote IR. Signal Enhancement of the Dentate Nucleus at Unenhanced MR Imaging after Very High Cumulative Doses of the Macrocyclic Gadolinium-based Contrast Agent Gadobutrol: An Observational Study. Radiology 2017;285:434-44
35. Splendiani A, Perri M, Marsecano C, et al. Effects of serial macrocyclic-based contrast materials gadoterate meglumine and gadobutrol administrations on gadolinium-related dentate nuclei signal increases in unenhanced T1-weighted brain: a retrospective study in 158 multiple sclerosis (MS) patients. Radiol Med 2017
36. Young JR, Orosz I, Franke MA, et al. Gadolinium deposition in the paediatric brain: T1-weighted hyperintensity within the dentate nucleus following repeated gadolinium-based contrast agent administration. Clin Radiol 2017
37. Bolles GM, Yazdani M, Stalcup ST, et al. Development of High Signal Intensity within the Globus Pallidus and Dentate Nucleus following Multiple Administrations of Gadobenate Dimeglumine. AJNR American journal of neuroradiology 2018
38. Moser FG, Watterson CT, Weiss S, et al. High Signal Intensity in the Dentate Nucleus and Globus Pallidus on Unenhanced T1-Weighted MR Images: Comparison between Gadobutrol and Linear Gadolinium-Based Contrast Agents. AJNR American journal of neuroradiology 2018
39. Lim WH, Choi SH, Yoo RE, et al. Does radiation therapy increase gadolinium accumulation in the brain?: Quantitative analysis of T1 shortening using R1 relaxometry in glioblastoma multiforme patients. PLoS One 2018;13:e0192838
40. Behzadi AH, Farooq Z, Zhao Y, Shih G, Prince MR. Dentate Nucleus Signal Intensity Decrease on T1-weighted MR Images after Switching from Gadopentetate Dimeglumine to Gadobutrol. Radiology 2018:171398
41. Hu HH, Pokorney A, Towbin RB, Miller JH. Increased signal intensities in the dentate nucleus and globus pallidus on unenhanced T1-weighted images: evidence in children undergoing multiple gadolinium MRI exams. Pediatr Radiol 2016;46:1590-8
42. Flood TF, Stence NV, Maloney JA, Mirsky DM. Pediatric Brain: Repeated Exposure to Linear Gadolinium-based Contrast Material Is Associated with Increased Signal Intensity at Unenhanced T1-weighted MR Imaging. Radiology 2016:160356
43. Roberts DR, Chatterjee AR, Yazdani M, et al. Pediatric Patients Demonstrate Progressive T1-Weighted Hyperintensity in the Dentate Nucleus following Multiple Doses of Gadolinium-Based Contrast Agent. AJNR American journal of neuroradiology 2016;37:2340-7
44. Radbruch A, Haase R, Kickingereder P, et al. Pediatric Brain: No Increased Signal Intensity in the Dentate Nucleus on Unenhanced T1-weighted MR Images after Consecutive Exposure to a Macrocyclic Gadolinium-based Contrast Agent. Radiology 2017:162980
45. Rossi Espagnet MC, Bernardi B, Pasquini L, Figa-Talamanca L, Toma P, Napolitano A. Signal intensity at unenhanced T1-weighted magnetic resonance in the globus pallidus and dentate nucleus after serial administrations of a macrocyclic gadolinium-based contrast agent in children. Pediatr Radiol 2017
46. Schneider GK, Stroeder J, Roditi G, et al. T1 Signal Measurements in Pediatric Brain: Findings after Multiple Exposures to Gadobenate Dimeglumine for Imaging of Nonneurologic Disease. AJNR American journal of neuroradiology 2017
47. Tibussek D, Rademacher C, Caspers J, et al. Gadolinium Brain Deposition after Macrocyclic Gadolinium Administration: A Pediatric Case-Control Study. Radiology 2017:161151
48. Renz DM, Kumpel S, Bottcher J, et al. Comparison of Unenhanced T1-Weighted Signal Intensities Within the Dentate Nucleus and the Globus Pallidus After Serial Applications of Gadopentetate Dimeglumine Versus Gadobutrol in a Pediatric Population. Investigative radiology 2017
49. Kinner S, Schubert TB, Bruce RJ, et al. Deep Brain Nuclei T1 Shortening after Gadobenate Dimeglumine in Children: Influence of Radiation and Chemotherapy. AJNR American journal of neuroradiology 2017
50. Tamrazi B, Nguyen B, Liu CJ, et al. Changes in Signal Intensity of the Dentate Nucleus and Globus Pallidus in Pediatric Patients: Impact of Brain Irradiation and Presence of Primary Brain Tumors Independent of Linear Gadolinium-based Contrast Agent Administration. Radiology 2017:171850
51. Ryu YJ, Choi YH, Cheon JE, et al. Pediatric Brain: Gadolinium Deposition in Dentate Nucleus and Globus Pallidus on Unenhanced T1-Weighted Images Is Dependent on the Type of Contrast Agent. Investigative radiology 2018
52. Kasper E, Schemuth HP, Horry S, Kinner S. Changes in signal intensity in the dentate nucleus at unenhanced T1-weighted magnetic resonance imaging depending on class of previously used gadolinium-based contrast agent. Pediatr Radiol 2018
53. Bhargava R, Persad ARL, Bhargava NK, Hawkes M. Multiple Administrations of Gadobutrol in the Pediatric Brain: No Change in T1 Signal at MRI. Radiology 2018:172988
54. Radbruch A, Haase R, Kickingereder P, et al. Pediatric Brain: No Increased Signal Intensity in the Dentate Nucleus on Unenhanced T1-weighted MR Images after Consecutive Exposure to a Macrocyclic Gadolinium-based Contrast Agent. Radiology 2017;283:828-36
55. Flood TF, Stence NV, Maloney JA, Mirsky DM. Pediatric Brain: Repeated Exposure to Linear Gadolinium-based Contrast Material Is Associated with Increased Signal Intensity at Unenhanced T1-weighted MR Imaging. Radiology 2017;282:222-8