

1 **Immediate Adverse Reactions and Anaphylaxis associated with gadolinium-based contrast agents in a patient**  
2 **with meningioma: case report and literature review**

3

4 **ABSTRACT**

5 Gadolinium chelates are relatively safe contrast media used in MRI. Immediate severe adverse effects are  
6 exceptionally rare. The incidence of immediate hypersensitivity reactions to MR contrast media was 0.079%, and the  
7 recurrence rate of hypersensitivity reactions was 30% in patients with previous reactions. The risk factors for  
8 immediate hypersensitivity reactions to MR contrast media were the female sex, allergies and asthma. We report a  
9 case of anaphylactic shock due to Gadobenedimeglumine. While undergoing a magnetic resonance imaging  
10 examination, 36 year-old female patient became severely hypotensive, lost consciousness, and had generalized  
11 erythema immediately after the intravenous injection of this product. She recovered rapidly after injection of  
12 epinephrine and her blood volume was restored with intravenous fluids. To our knowledge and according to  
13 literatures, there was not any correlation with underlying disease and there is no report in meningioma.

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15 **Keywords:** gadolinium; magnetic resonance, contrast agents, contrast enhancement, adverse reaction, Anaphylaxis

16

17 **INTRODUCTION**

18 Magnetic resonance imaging (MRI) has proved to be a valuable diagnostic modality for central nervous  
19 system (CNS) disease. Although intrinsic tissue contrast is high, administration of intravenous contrast media has  
20 been shown to improve both lesion detection and differential diagnosis. The largest class of contrast media in use  
21 today in MRI, both in terms of number of doses and number of agents, is the gadolinium chelates (12).

22 Allergic-like reactions to IV gadolinium containing contrast agents, although relatively rare, do occur (4).

23 Gadolinium chelates are relatively safe contrast media used in MRI. Immediate severe adverse effects are  
24 exceptionally rare and mostly concern mild anaphylactic reactions (6).

25 Acute adverse reactions related to gadopentetate dimeglumine and gadobenedimeglumine were rare. When they  
26 occurred, most of the reactions were mild, although moderate and severe reactions did occur (1).

27 Gadobenedimeglumine is currently approved for clinical use throughout Europe but not in the United States.

28 Gadobenedimeglumine has two characteristics that distinguish it from other gadolinium chelates with  
29 extracellular distribution and renal excretion currently available in the United States and worldwide. A small  
30 percentage of the agent is excreted via the hepatobiliary system in addition to renal excretion, as with the other  
31 gadolinium chelates (9, 8, and 14).

32 Safety assessments have indicated similar safety profiles for gadobenedimeglumine and other gadolinium-based  
33 contrast agents, the reported overall incidence of adverse events being less than 0.03% in postmarketing surveillance  
34 (13).

35 The incidence of immediate hypersensitivity reactions to MR contrast media was 0.079%, and the recurrence rate of  
36 hypersensitivity reactions was 30% in patients with previous reactions. The risk factors for immediate

37 hypersensitivity reactions to MR contrast media were the female sex, allergies and asthma. The incidence of  
38 immediate hypersensitivity reactions increased depending on the number of exposures to MR contrast media.

39 Gadodiamide had the lowest rate (0.013%) of immediate hypersensitivity reactions, while gadobenedimeglumine  
40 had the highest rate (0.22%). The appropriate premedication with antihistamine or systemic corticosteroid should be  
41 considered according to the severity of the previous hypersensitivity reactions (5).

42 Allergic-like reactions were classified as mild, moderate, or severe. Mild allergic-like reactions were characterized  
43 by one or more of the following: hives, pruritus, localized facial edema, nasal congestion, sneezing, and "scratchy

44 throat." Moderate allergic like reactions were characterized by one or more of the following: diffuse erythema,  
45 dyspnea, wheezing, stridor, or emergency department transfer. Severe allergic-like reactions were characterized by

46 one or more of the following: severe laryngeal edema, cardiopulmonary collapse, anaphylactoid shock, or hospital

47 admission. Physiologic reactions (e.g., vasovagal reactions, nausea, vomiting) and contrast medium extravasations  
48 were not analyzed because they are not allergic like reactions (3).

49 The decision to use one gadolinium-based contrast product over another has become more complicated and  
50 increasingly important. When prescribing gadolinium-based contrast agents, radiologists need to consider not only  
51 the risk of NSF but also the risk of acute adverse reactions (1).

52 Of these adverse events, 69% were nausea, vomiting, or ipsilateral arm coolness during the contrast injection (9).  
53 We have recommended in our practice that patients with a prior history of reaction to iodinated contrast media be  
54 closely observed during gadolinium administration. Premedication with steroids and histamine blocking agents may  
55 be considered in patients who had severe reactions to iodinated contrast media, although the usefulness or necessity  
56 of such premedication has not yet. Among patients with a history of prior adverse response to gadolinium-based MR  
57 Imaging contrast media, the repeated use of such agents should also be carefully considered. Among these patients,  
58 pre-treatment with corticosteroids and the administration of a different gadolinium-based contrast agent may be  
59 useful. (9).

60 Allergic-like reactions to gadolinium-containing contrast media can occur despite premedication with corticosteroids  
61 and antihistamines (4).

62 Gadolinium chelates in appropriate volumes are useful alternative contrast media in selected high-risk patients  
63 undergoing angiographic studies (15).

64 To the best of our knowledge, the first reported use of a gadolinium chelate for intraarterial DSA was by Kinno et al  
65 in 1993 in a patient with a severe allergy to iodinated contrast media (7).

66  
67 To our knowledge and according to literatures, there was not any correlation with underlying disease and there is no  
68 report in meningioma.

69 We report a case of anaphylactic shock due to Gadobenedimeglumine. While undergoing a magnetic resonance  
70 imaging examination, 36-year-old female patient became severely hypotensive, lost consciousness, and had  
71 generalized erythema immediately after the intravenous injection of this product. She recovered rapidly after  
72 injection of epinephrine and her blood volume was restored with intravenous fluids.

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#### 74 **CASE report**

75 A 36-year-old female patient with a personal history of headache, while undergoing MRI scans, developed  
76 bronchospasm in the first minute of Gadolinium infusion. She became severely hypotensive, lost consciousness, and  
77 had generalized erythema immediately after the intravenous injection of this product. The procedure was cancelled  
78 and acute treatment of the reaction took place. The patient reported 2 additional MRI scans with definite use of  
79 unknown contrast media in the past 2 months with the same adverse effect that was not noted before performing  
80 MRI in our center.

81 Within 5 minutes of MR contrast IV injection; the patient suffered severe cardiovascular collapse. MRI procedure  
82 was aborted and administration of Gadolinium discontinued. Aggressive IV fluid resuscitation and IV epinephrine  
83 administration were necessary to re-establish cardiovascular stability. Some periorbital and labial oedema were  
84 noted.

85 She had no prior history of allergies and asthma.

86 She recovered rapidly after she was given injection of epinephrine and her blood volume was restored with  
87 intravenous fluids.

88 MRI revealed meningioma (Fig 1). She was admitted to our neurosurgery department. Surgical resection was  
89 performed. The postoperative period was uneventful and during the early postoperative period had resolution of  
90 symptoms.

91

#### 92 **DISCUSSION**

93 Gadolinium chelates are being increasingly used in clinical MRI practice for a wide spectrum of disease processes  
94 and types of exams (12).

95 The incidence of adverse reactions is relatively low compared with that of contrast agents used for CT  
96 Gadolinium-based contrast agents used as medical imaging agents, can cause life-threatening or fatal anaphylaxis.  
97 There were differences in disproportionality of reporting between agents. Although differences in numbers of  
98 reports of anaphylaxis reflect relative utilization rates of the various agents, disproportionality analyses disclose  
99 significant safety signals of anaphylaxis associated with most gadolinium-based contrast agents (11).

100 All gadolinium-based contrast agent adverse events reported to radiology quality assurance committees were graded  
101 according to American College of Radiology criteria and divided by the total number of injections to determine  
102 incidence during the past 10 years (10).

103 Adverse events were more likely in women, with a female to male ratio of 3.3, and in patients with history of prior  
104 allergic reactions ( $p < 0.001$ ). Gadobenedimeglumine had more severe patient reactions, including arrest (defined  
105 as the patient becoming unresponsive and the code team being called) and death. From 2004 to 2009, the FDA  
106 received reports on 40 gadolinium-based contrast agent U.S. deaths unrelated to nephrogenic systemic fibrosis (10).

107 Gadolinium-based contrast agents are very safe, with only rare reports of death, and raises the possibility that  
108 nonionic linear gadolinium-based contrast agents and gadopentetate dimeglumine may have fewer severe immediate  
109 adverse events compared with gadobenedimeglumine (10).

110 Gadobenedimeglumine is comparable to gadodiamide in terms of safety and efficacy for imaging of CNS lesions,  
111 with a possible advantage in imaging applications owing to enhanced T1 relaxivity. This effect is thought to be due  
112 to mild protein binding. The clinical availability of gadobenedimeglumine will add another valuable tool to the  
113 armamentarium of the diagnostic radiologist. (12).

114 The indexes of suspicion for the occurrence of reactions to gadolinium, and both the documentation and the  
115 management of adverse reactions, must be as rigorous for reactions associated with MR imaging contrast agents as  
116 they are for reactions associated with iodinated contrast media (9).

117 After gadobenedimeglumine was substituted for gadopentetate dimeglumine, a significant transient increase  
118 occurred in the frequency of reported allergic-like reactions that demonstrated a temporal pattern suggestive of the  
119 Weber effect (a transient increase in adverse event reporting that tends to peak in the 2nd year after a new agent or  
120 indication is introduced).(3)

121 Although gadolinium is a safe contrast medium, anaphylactoid reactions do occur. Some are severe. Reactions to  
122 MR imaging contrast media are uncommon enough that radiologists may not be as familiar with their management  
123 as they are with the treatment of complications associated with iodinated radiographic contrast media. Personnel must  
124 be trained and equipment for the management or resuscitation of patients experiencing reactions to  
125 gadolinium contrast media must be available at both hospital-based and freestanding facilities. Gadolinium has  
126 physical properties that are well suited for radiographic imaging. DSA with a gadolinium chelate as contrast medium  
127 can provide images of suitable quality for diagnosis and intervention. The overall safety profile of gadolinium-based  
128 contrast media is excellent (15).

129 With the introduction of the most recent MR contrast agent approved for use in the United States, our interest in its  
130 substantial potential clinical benefits that would result from its increased relaxivity was balanced by concern that the  
131 rate of adverse effects may increase. This concern has been ameliorated with the findings of rates of adverse  
132 reactions that are comparable to those published for other MR contrast agents (2).

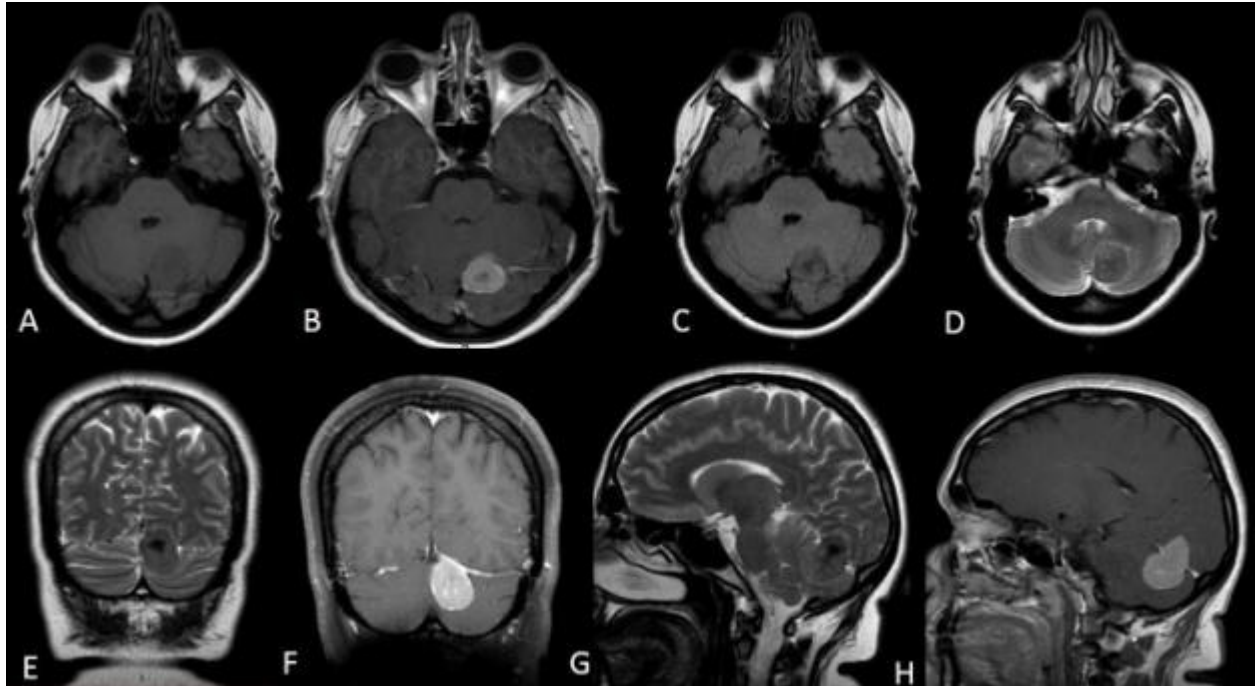
133 Although gadolinium-based contrast agents are extremely safe, death from hypersensitivity reactions and  
134 debilitating fibrosis are possible. These can be minimized by the skill and vigilance of the radiologist and MRI team  
135 (10).

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178 Fig 1: Preoperative MR imaging for a 36-year-old woman with tentorial meningioma. MRI demonstrated  
179 a large left medial tentorial meningioma extending along tentorium with supra and infra- tentorium  
180 components, causing significant mass effect on these structures without early signs of hydrocephalus.  
181 Axial (A) T1, (B) enhanced T1, (C) FLAIR, (D) T2; coronal (E) T2, (F) enhanced T1; sagittal (G) T2, (H)  
182 enhanced T1 MRI.



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