

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

4 ABSTRACT

5 Object. 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.

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

13 Conclusions. Although gadolinium is a safe contrast medium, anaphylactoid reactions do occur. Some are severe.
14 Reactions to MR imaging contrast media are uncommon enough that radiologists may not be as familiar with their
15 management as they are with the treatment of complications associated with iodinated radiographic contrast media.
16 Gadobenatidimeglumine is comparable to gadodiamide in terms of safety and efficacy for imaging of CNS lesions.

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

20 INTRODUCTION

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

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

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

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

30 Gadobenatidimeglumine is currently approved for clinical use throughout Europe but not in the United States.

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

35 Safety assessments have indicated similar safety profiles for gadobenatidimeglumine and other gadolinium-based
36 contrast agents, the reported overall incidence of adverse events being less than 0.03% in postmarketing surveillance
37 (13).

38 The incidence of immediate severe hypersensitivity reactions to MR contrast media was 0.079%, and the recurrence
39 rate of hypersensitivity reactions was 30% in patients with previous reactions. The risk factors for immediate
40 hypersensitivity reactions to MR contrast media were the female sex, allergies and asthma. The incidence of
41 immediate hypersensitivity reactions increased depending on the number of exposures to MR contrast media.
42 Gadodiamide had the lowest rate (0.013%) of immediate hypersensitivity reactions, while gadobenatidimeglumine
43 had the highest rate (0.22%). The appropriate premedication with antihistamine or systemic corticosteroid should be
44 considered according to the severity of the previous hypersensitivity reactions (5).

45 Allergic-like reactions were classified as mild, moderate, or severe. Mild allergic-like reactions were characterized
46 by one or more of the following: hives, pruritus, localized facial edema, nasal congestion, sneezing, and “scratchy
47 throat.” Moderate allergic like reactions were characterized by one or more of the following: diffuse erythema,
48 dyspnea, wheezing, stridor, or emergency department transfer. Severe allergic-like reactions were characterized by
49 one or more of the following: severelaryngeal edema, cardiopulmonary collapse, anaphylactoid shock, or hospital
50 admission. Physiologic reactions (e.g., vasovagal reactions, nausea, vomiting) and contrast medium extravasations
51 were not analyzed because they are not allergic like reactions (3).

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

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

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

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

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

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

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

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76 **CASE report**

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

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

87 She had no prior history of allergies and asthma. She had no comorbidities and past medical history was
88 negative.

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

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

94

95 **DISCUSSION**

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

98 The incidence of adverse reactions is relatively low compared with that of contrast agents used for CT
99 Gadolinium-based contrast agents used as medical imaging agents, can cause life-threatening or fatal anaphylaxis.

100 There were differences in disproportionality of reporting between agents. Although differences in numbers of
101 reports of anaphylaxis reflect relative utilization rates of the various agents, disproportionality analyses disclose
102 significant safety signals of anaphylaxis associated with most gadolinium-based contrast agents (11).

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

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

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

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

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

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

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

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

136 Although gadolinium-based contrast agents are extremely safe, death from hypersensitivity reactions and
137 debilitating fibrosis are possible. These can be minimized by the skill and vigilance of the radiologist and MRI team
138 (10).

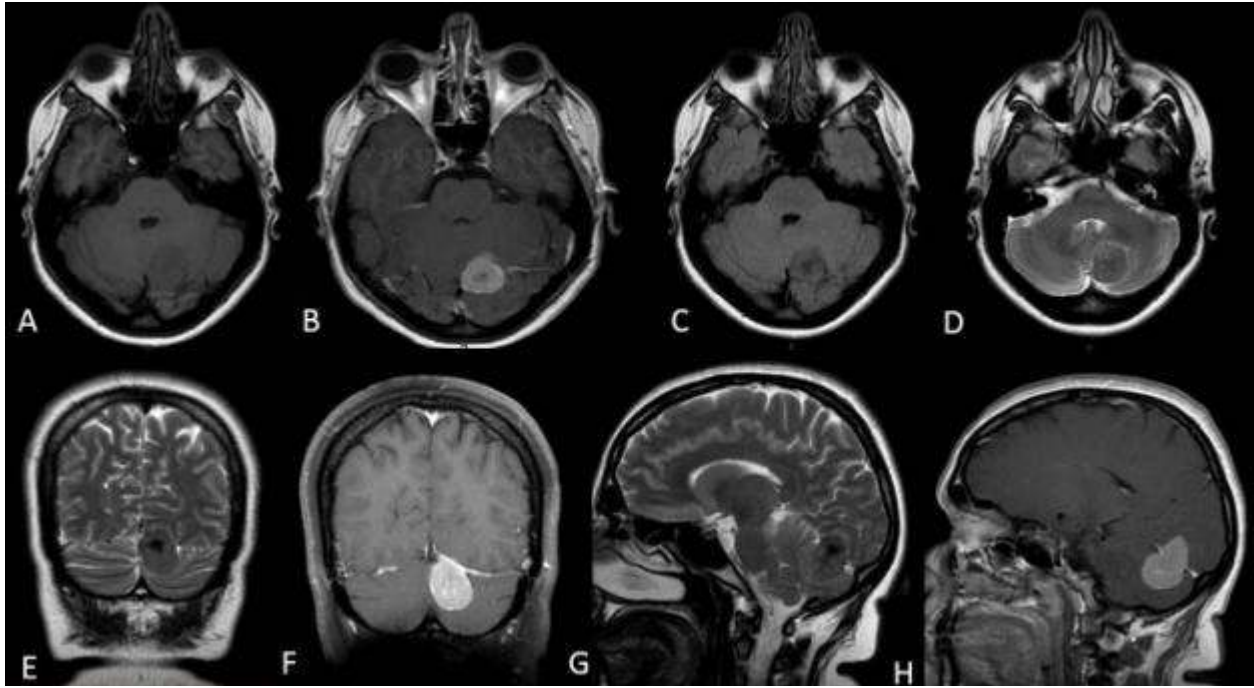
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141 **management as they are with the treatment of complications associated with iodinated radiographic contrast media.**
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Fig 1: Preoperative MR imaging for a 36-year-old woman with tentorial meningioma. MRI demonstrated a large left medial tentorial meningioma extending along tentorium with supra and infra-tentorium components, causing significant mass effect on these structures without early signs of hydrocephalus. Axial (A) T1, (B) enhanced T1, (C)FLAIR, (D) T2; coronal (E) T2, (F) enhanced T1; sagittal (G)T2, (H) enhanced T1 MRI.