Immediate Hypersensitivity Reaction to Gadolinium-based MR Contrast Media[1]

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Purpose: To determine the incidence and risk factors of immediate hypersensitivity reactions to gadolinium-based magnetic resonance (MR) contrast agents.

Materials and Methods: Institutional review board approval and a waiver of informed consent were obtained. A retrospective study of patients who had been given gadolinium-based MR contrast media between August 2004 and July 2010 was performed by reviewing their electronic medical records. In addition to data on immediate hypersensitivity reaction, the kinds of MR contrast media and demographic data including age, sex, and comorbidity were collected. To compare the groups, the χ^2 test, Fisher exact test, χ^2 test for trend, Student t test, analysis of variance test, and multiple logistic regression test were performed.

Results: A total of 112 immediate hypersensitivity reactions (0.079% of 141 623 total doses) were identified in 102 patients (0.121% of 84 367 total patients). Among the six evaluated MR contrast media, gadodiamide had the lowest rate (0.013%) of immediate hypersensitivity reactions, while gadobenate dimeglumine had the highest rate (0.22%). The rate for immediate hypersensitivity reactions was significantly higher in female patients (odds ratio = 1.687; 95% confidence interval: 1.143, 2.491) and in patients with allergies and asthma (odds ratio = 2.829; 95% confidence interval: 1.427, 5.610). Patients with a previous history of immediate hypersensitivity reactions had a higher rate of recurrence after reexposure to MR contrast media (30%) compared with the incidence rate in total patients ($P < .0001$). The incidence of immediate hypersensitivity reactions increased depending on the number of times patients were exposed to MR contrast media (P for trend = .036). The most common symptom was urticaria (91.1%), and anaphylaxis occurred in 11 cases (9.8%). The mortality rate was 0.0007% because of one fatality.

Conclusion: The incidence of immediate hypersensitivity reactions to MR contrast media was 0.079%, and the recurrence rate of hypersensitivity reactions was 30% in patients with previous reactions.

Supplemental material: *http://radiology.rsna.org/lookup/suppl/doi:10.1148/radiol.12112025/-/DC1*

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During the past 3 decades, magnetic resonance (MR) contrast media have been recognized to have superb safety profiles with almost no side effects. Therefore, MR imaging has been routinely used as a safe alternative modality to computed tomographic (CT) scans in patients with hypersensitivity to CT contrast media (1). However, nephrogenic systemic fibrosis due to MR contrast media has been reported (2,3). Cases of severe immediate hypersensitivity reactions such as anaphylaxis to MR contrast media also have been reported (4–6). Because the use of MR imaging has increased, several investigations on the safety of MR contrast media have been done (1,7–11).

Advances in Knowledge

- The incidence of immediate hypersensitivity reactions to MR contrast media was 0.079% per dose and 0.121% per person.
- The recurrence rate of immediate hypersensitivity reactions to gadolinium-based MR contrast media was 30% (eight of 27) in patients who previously had immediate hypersensitivity reactions to MR contrast media.
- The risk factors for immediate hypersensitivity reactions to MR contrast media in our study were the female sex (odds ratio = 1.687; 95% confidence interval: 1.143, 2.491) and allergies and asthma (odds ratio = 2.829; 95% confidence interval: 1.427, 5.610).
- The incidence of immediate hypersensitivity reactions increased depending on the number of exposures to MR contrast media (0.105%, 0.137%, and 0.171% for one, two, and three or more exposures, respectively).
- Among the six evaluated MR contrast media, gadodiamide had the lowest rate (0.013%) of immediate hypersensitivity reactions, while gadobenate dimeglumine had the highest rate (0.22%).

According to studies on the adverse reactions to MR contrast media, the rate of incidence for acute adverse reactions after injection of MR contrast media varied from 0.17% to 2.4% (9). This is much lower than the rate of incidence for acute adverse reactions associated with low-osmolar nonionic iodinated contrast media used for CT scans, and MR gadolinium-based contrast agents are considered relatively safe (1,7,8,12).

Adverse events after injection of the contrast media can be divided into three different types: toxic reactions, immediate hypersensitivity reactions, and events unrelated to the exposure of contrast material itself such as a vasovagal reaction (13). Immediate hypersensitivity reactions occur within 1 hour after administration of the contrast media. Although the most common immediate hypersensitivity symptoms are mild pruritus and urticaria, more severe reactions involving the cardiovascular and respiratory systems can occur (14). Most previous studies have included all types of adverse reactions other than immediate hypersensitivity reactions. Until now, there have been few studies on the incidence and risk factors of immediate hypersensitivity reactions to MR contrast media (1,12).

It is almost impossible to predict which patients are more susceptible to acute adverse reactions to MR contrast media, and recognizing adverse reactions is relatively difficult because patients are positioned for a considerable time inside the bore of an MR imager, which is physically remote from the technologist or supervising physician at the time an adverse reaction begins. In addition, the exact mechanism and risk factors of hypersensitivity reactions are unknown. To protect patients from the potential risk of immediate hypersensitivity reactions to MR contrast media, more detailed studies based on large clinical data sets are necessary.

The purpose of this study was to investigate the incidence and risk factors of immediate hypersensitivity reactions to gadolinium-based MR contrast agents.

Implication for Patient Care

- The recurrence reactions occurred in 30% of patients who previously had immediate hypersensitivity reactions to MR contrast media; therefore, the appropriate premedication with antihistamine or systemic corticosteroid should be considered according to the severity of the previous hypersensitivity reactions.

Materials and Methods

Study Subjects

This study was approved by the institutional review board of Seoul National University Hospital, and informed consent was waived. All cases that used gadolinium-based MR contrast media for MR imaging at Seoul National University Hospital between August 1, 2004, and July 31, 2010, were reviewed. The demographic data, comorbid disease data, and prescribed medication data were extracted from the electronic medical record. To retrieve data on immediate hypersensitivity reactions, all medical records written by physicians, nurses, and radiology technicians were searched with terms possibly related to immediate hypersensitivity reactions, such as pruritus, skin rash, and urticarial, and with terms for respiratory symptoms. The medical records contained

Published online before print
10.1148/radiol.12112025 **Content code:** MR

Radiology 2012; 264:414–422

Author contributions:
Guarantors of integrity of entire study, H.R.K., M.H.K., W.L., K.U.M., S.H.C.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, J.W.J., H.R.K., W.L., K.U.M., S.H.C.; clinical studies, J.W.J., H.R.K., M.H.K., W.L., K.U.M., S.H.C.; statistical analysis, J.W.J., H.R.K., W.L., K.U.M., S.H.C.; and manuscript editing, J.W.J., H.R.K., W.L., K.U.M., M.H.H., S.H.C.

Potential conflicts of interest are listed at the end of this article.

the onset, signs, symptoms, and management, including medications prescribed when immediate hypersensitivity reactions developed. The screened data were first intensively reviewed by two adverse-reaction monitoring nurses and then confirmed by two allergist physicians (S.H.C. and H.R.K., with 18 and 9 years of experience in the field of allergy, respectively).

Demographic data on the study population were collected, including age, sex, and comorbidity, on the basis of the *International Classification of Diseases, 10th Revision*. In addition, the latest laboratory results such as white blood cell and eosinophil counts, alanine aminotransferase level, and creatinine level within 1 month before exposure to each MR contrast agent were collected. To evaluate renal function, the estimated glomerular filtration rate was determined by using the Modification of Diet in Renal Disease Study method (15).

In patients with hypersensitivity reactions, data on premedication administered on the day of the reexposure to MR contrast media were extracted. In addition, the medical records of 500 randomly selected subjects from the group without immediate hypersensitivity reactions were screened about premedication. To determine the previous history of exposure to MR contrast media before the study period, data from January 2000 to July 2004 were also searched, and the number of exposures to MR contrast media and the different kinds of MR contrast media that a patient was exposed to were reviewed (Fig 1).

The following gadolinium-based contrast media were utilized: *(a)* macrocyclic agents including ionic gadoteric acid (Dotarem; Guerbet, Roissy, France) and nonionic gadobutrol (Gadovist; Bayer Schering Pharma, Berlin, Germany) and *(b)* linear agents including ionic agents gadopentetate dimeglumine (Magnevist; Bayer Schering Pharma), gadobenate dimeglumine (MultiHance; Bracco Diagnostics, Milan, Italy), and gadoxetic acid (Primovist; Bayer Schering Pharma) and the nonionic agent gadodiamide (Omniscan; GE Healthcare, Oslo, Norway).

Figure 1

The extracted variables
Sex
Age
Underlying disease
Laboratory finding (white blood cell counts, eosinophil counts, alanine aminotransferase level, creatinine level)
Estimated glomerular filtration rate
Type of MR contrast media
Number of previous exposures to MR contrast media
Immediate hypersensitivity reactions
• Signs and symptoms
• Management for hypersensitivity reaction
• Use of β-blocker
• Severity of immediate hypersensitivity reactions
• Pre- and postmedication on the day of MR contrast medium injection
• Recurrence after reexposure to MR contrast media
The analyses
Incidence of immediate hypersensitivity reactions
Incidence of immediate hypersensitivity reactions according to number of exposures
Comparison of the incidence of immediate hypersensitivity reactions according to specific agent, molecular structure, and ionic character of MR contrast media
Comparison of parameters according to development and severity of immediate hypersensitivity reactions
Comparisons of parameters according to recurrence of immediate hypersensitivity reaction to MR contrast media

Figure 1: List of extracted variables from electronic medical records and analyses. Estimated glomerular filtration rate was calculated by using the Modification of Diet in Renal Disease Study method (15).

Definition of Immediate Hypersensitivity Reactions to MR Contrast Media

Immediate hypersensitivity reactions were defined as cases in which allergy-like symptom(s), such as urticaria, angioedema, bronchospasm, and anaphylaxis, developed within 1 hour after injection of the contrast media. Simple nausea, vomiting, sweating, warmth, anxiety, and reactions involving the site of injection such as pain and burning sensations were excluded when they were not accompanied by other symptoms that suggested immediate hypersensitivity reactions. Reported hypersensitivity symptoms were assessed by two allergy specialists on the basis of the World Health Organization-Uppsala Monitoring Centre causality assessment algorithm (16,17). Cases evaluated as certain or probable were considered to have a causal relationship with the administered MR contrast medium.

The severity of the hypersensitivity reactions was classified into three categories by following the guidelines in *ACR Manual on Contrast Media* (18). A mild reaction was self-limited with signs and symptoms showing no evidence of progression and included simple rashes, hives, coughing, and swelling of the eyes and face. A moderate reaction had more pronounced symptoms to a moderate degree and included bronchospasm, laryngeal edema, and generalized erythema. A severe reaction was life threatening and included severe laryngeal edema, convulsions, profound hypotension, unresponsiveness, arrhythmia, and cardiopulmonary arrest. Diagnosis of anaphylaxis was made according to the international diagnostic criteria updated in 2006 (19). Anaphylaxis was defined as a rapid onset, severe, potentially fatal, systemic allergic reaction after exposure to MR contrast media with any one of the following three

conditions: *(a)* respiratory compromise or reduced blood pressure with skin or mucosal reactions; *(b)* presenting with more than two of any of the following reactions: skin-mucosal reactions, respiratory compromise, reduced blood pressure, and persistent gastrointestinal symptoms; and *(c)* an acute hypotensive episode in a patient with known allergies to MR contrast media. A vasovagal reaction was differentiated from anaphylaxis by the frequently accompanied bradycardia and no combined allergic symptoms.

Statistical Analysis

Software (SPSS, version 17.0; SPSS, Chicago, Ill) was used for statistical analysis. The analyzed items are summarized in Figure 1. The incidence of immediate hypersensitivity reactions to MR contrast media was calculated. To compare the hypersensitivity reaction group to the group without hypersensitivity reaction, the χ^2 test, Fisher exact test, and Student t test were used. To evaluate the trend for the male proportion according to the severity and the incidence of immediate hypersensitivity reactions according to the number of exposures to MR contrast media, the χ^2 test for trend was used. To compare the parameters according to the severity of the immediate hypersensitivity reactions, the analysis of variance test was used. Multiple logistic regression analysis for sex, age, allergic disease, type of MR contrast media, and number of previous exposures to MR contrast media was performed to identify the risk factors related to immediate hypersensitivity reactions to MR contrast agents, and the results were presented as odds ratios and 95% confidence intervals. A P value less than .05 was considered to indicate a significant difference.

Results

Incidence of Immediate Hypersensitivity Reactions to MR Contrast Media

A total of 141 623 MR examinations with MR contrast media were performed in 84 367 patients during a 6-year period. The numbers of exposures to MR contrast media varied from one to 54, and the mean was 1.7 exposures per person. A total of 72.2% of the study subjects (60 925) were exposed to gadolinium-based contrast media only one time.

There were 148 acute reactions, of which 36 cases of vomiting, nausea, and pain at the injection site were excluded. The incidence of immediate hypersensitivity reactions was 0.079% (112 of 141 623) (Fig 2). These occurred in 0.121% (102 of 84 367) of patients.

Immediate Hypersensitivity Reaction Rates according to MR Contrast Agent

Gadobenate dimeglumine had the highest incidence of immediate hypersensitivity reactions (14 [0.22%] of 6361), followed by gadoxetic acid (six [0.116%] of 5152), gadobutrol (33 [0.099%] of 33 242), gadoteric acid (31 [0.080%] of 38 580), gadopentetate (26 [0.061%] of 42 323), and gadodiamide (two [0.013%] of 15 959) (Fig 2) ($P < .0001$).

There was no significant difference in the incidence of reactions according to the molecular structure of the contrast agents (64 [0.089%] of 71 822 in macrocyclic agents and 48 [0.069%] of 69 801 in linear agents) or the ionicity (77 [0.083%] of 92 345 in ionic agents and 35 [0.071%] of 49 201 in nonionic agents). Among the linear agents, ionic agents had a higher incidence of immediate hypersensitivity reactions than nonionic agents (0.085% vs 0.013%, P = .0004), but the presence or absence of ionicity did not affect the incidence rate among the macrocyclic agents.

The proportion of subjects exposed to gadobenate dimeglumine was significantly higher and the proportion of subjects exposed to gadodiamide was significantly lower in the immediate hypersensitivity reactions group than in the group without immediate hypersensitivity reactions (Table 1).

Clinical Characteristics

The incidence of immediate hypersensitivity reactions was 0.098% in women (73 of 74 066), which was almost double the rate in men (39 [0.058%] of 67 557, P = .006) (Table 1). The proportion of female patients was significantly higher in the group with immediate hypersensitivity reactions than in the group without immediate hypersensitivity reactions (65.2% vs 52.3%, P = .006). The mean age was not different between the two groups. Laboratory data were available in 121 395 patients (85.7%). There was no significant difference in total white blood cell and

Figure 2

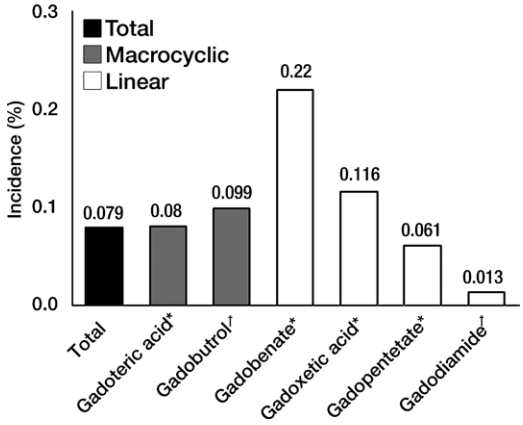

Figure 2: Graph shows incidence of immediate hypersensitivity reactions to MR contrast media, which was 0.079% of the total doses administered. Gadobenate dimeglumine had the highest rate of incidence (0.22%), and gadodiamide had the lowest (0.013%). * = ionic agent, † = nonionic agent.

Table 1

Comparison between Cases with and Cases without Immediate Hypersensitivity Reactions

Parameter	No Immediate Hypersensitivity Reaction (n = 141 511)	Immediate Hypersensitivity Reaction (n = 112)	P Value
Female patients	73 993 (52.3)	73 (65.2)	.006
Age (y)*	50.18 ± 20.77	51.21 ± 16.10	.498
White blood cell count (per microliter)*	6974.94 ± 4901.65	6180.00 ± 2411.11	.112
Eosinophil count (per microliter)*	174.03 ± 266.86	148.56 ± 116.83	.352
Creatinine level (mg/dL)*	0.93 ± 0.55	0.90 ± 0.20	.641
Alanine aminotransferase level (IU/L)*	27.98 ± 57.33	28.85 ± 35.37	.881
No. of previous exposures to MR contrast media*	1.62 ± 3.11	1.65 ± 2.86	.912
No. of previous exposures to the identical contrast media*	1.09 ± 0.81	0.81 ± 1.70	.226
Type of MR contrast media			
Gadoteric acid	38 549 (27.2)	31 (27.7)	.917
Gadobutrol	33 209 (23.5)	33 (29.5)	.134
Gadobenate dimeglumine	6347 (4.5)	14 (12.5)	<.0001
Gadoxetic acid	5152 (3.6)	6 (5.4)	.332
Gadopentetate dimeglumine	42 297 (29.9)	26 (23.2)	.123
Gadodiamide	15 957 (11.3)	2 (1.8)	.0002

Note.—Unless otherwise indicated, data are numbers of cases, with percentages in parentheses.

* Data are means ± standard deviations.

eosinophil counts, alanine aminotransferase level, and creatinine level between the two groups. There was no significant difference in the number of previous exposures to MR contrast media or in the number of previous exposures to a specific type of contrast media between the two groups.

In terms of underlying diseases, the presence of hypertension and diabetes did not affect the incidence of immediate hypersensitivity reactions (P = .468 and .842, respectively). However, allergic diseases such as asthma, allergic rhinitis, chronic urticaria, food allergies, and drug hypersensitivity were more frequent in the group with immediate hypersensitivity reactions than in the group without immediate hypersensitivity reactions (P = .002) (Table 2).

Multiple logistic regression analysis showed significant results for female sex (P = .009; odds ratio = 1.687; 95% confidence interval: 1.143, 2.491), allergies and asthma (P = .003; odds ratio = 2.829; 95% confidence interval: 1.427, 5.610), gadobenate dimeglumine (P = .0002; odds ratio = 3.003; 95% confidence interval: 1.701, 5.303), and gadodiamide (P = .004; odds ratio = 0.122; 95% confidence interval: 0.029, 0.520).

Symptoms

Among the 112 hypersensitivity reactions, urticaria was the most common symptom observed in 102 cases (91.1%). Respiratory symptoms occurred in seventeen cases (15.2%); hypotension was observed in 11 cases (9.8%), and angioedema was observed in six cases (5.4%). Nineteen cases (17.0%) had multiple symptoms.

Eleven severe hypersensitivity reactions occurred in 10 patients, and all of them met the diagnostic criteria for anaphylaxis. Detailed clinical characteristics of each case of anaphylaxis are presented in Table E1 (online). Hypotension was present in all cases, respiratory symptoms in 10 cases (91%), and cutaneous manifestations in seven cases (64%).

One fatality occurred in a 76-year-old woman who developed the following symptoms: hypotension, dyspnea, nausea, and decreased consciousness after gadobutrol injection, and she died despite prompt cardiopulmonary resuscitation. The mortality rate was 0.0007%. In a patient who had experienced MR contrast media–induced anaphylaxis, anaphylaxis recurred when he was exposed to a different MR contrast material, with antihistamine as a premedication 51 days after his first anaphylactic episode.

In six of 11 cases, low blood pressure was quickly recovered with only prompt massive hydration. Three of the 11 cases of anaphylaxis were treated with epinephrine, and two cases were managed with other vasopressors such as dopamine and norepinephrine. In addition, four patients with respiratory distress were treated with β_2 agonist inhalation.

In the 102 patients who had immediate hypersensitivity reactions for the first time, more than half of the patients (60 patients, 58.8%) had hypersensitivity symptoms at their first exposure to MR contrast media. However, 42 patients (41.2%) had already been exposed to MR contrast media before the development of immediate hypersensitivity reactions, including 28 patients (27.5%) who had been exposed to exactly the same MR contrast agent. Chart review showed that premedication such as antihistamine or systemic steroid was not administered

Table 2

Comparison of Combined Allergic Diseases between Patients with and Those without Immediate Hypersensitivity Reactions

Disease	No Immediate Hypersensitivity Reaction (n = 84 265)	Immediate Hypersensitivity Reaction (n = 102)	P Value
Asthma	1322 (1.6)	3 (2.9)	.216
Allergic rhinitis	1258 (1.5)	3 (2.9)	.196
Food allergy	35 (0.0)	0 (0)	.959
Latex allergy	3 (0.0)	0 (0)	.996
Drug hypersensitivity	51 (0.1)	2 (2)	.002
Chronic urticaria	347 (0.4)	2 (2)	.015
Any of the above allergic disease	2728 (3.2)	10 (9.8)	.002

Note.—Data are numbers of cases, with percentages in parentheses.

when hypersensitivity reactions developed for the first time. No one was premedicated before the administration of MR contrast media in subjects selected from the group without immediate hypersensitivity reactions.

Clinical Characteristics according to Immediate Hypersensitivity Reaction Severity

Mild reactions (83.0%) were predominant, followed by severe and moderate reactions at the rate of 9.8% and 7.1%, respectively (Table 3). The incidence of mild, moderate, and severe reactions was 0.066%, 0.006%, and 0.008%, respectively.

The proportion of male patients experiencing immediate hypersensitivity reactions increased as the severity of the reactions increased (29.0%, 50.0%, and 72.7% in the order of mild, moderate, and severe reaction, respectively), and a linear trend was observed according to the severity (P for trend = .003). The incidence of severe immediate hypersensitivity reactions was three times higher in men (0.012%) than in women (0.004%) (Table 4).

However, age, underlying diseases, leukocyte counts, use of β-blockers, and use of different kinds of contrast media did not have any significant effect on the severity of the immediate hypersensitivity reactions. Creatinine levels were within normal range, and the estimated glomerular filtration rates were not different among the three groups for severity.

Frequency of MR Contrast Media Exposure and Incidence of Immediate Hypersensitivity Reactions to MR Contrast Media

The incidence of immediate hypersensitivity reactions was 0.105% (61 of 57 966 patients) for one exposure, 0.137% (17 of 12 381 patients) for two exposures, and 0.171% (24 of 14 020 patients) when exposed three times or more (P for trend = .036). This trend was maintained in patients with a mild reaction (P for trend = .017) but not in patients with moderate or severe reactions (Fig 3).

In patients who had previous immediate hypersensitivity reactions, the overall recurrence rate of immediate hypersensitivity reactions to the MR contrast media was 30% (eight of 27), and it was markedly higher than the incidence in total patients (0.121%, $P <$ .0001). Among 10 cases with recurrent hypersensitivity reactions, six patients experienced one recurrent reaction and two patients experienced two recurrent reactions.

Among the 27 patients with known immediate hypersensitivity reactions who were reexposed to MR contrast media after previous immediate hypersensitivity reactions, age (54 years vs 49 years), sex (female, 50% vs 47.4%), allergies and asthma (25% vs 5.3%), number of previous exposures to MR contrast media (2.13 vs 3.21), and the time interval between the immediate hypersensitivity reactions and reexposure (189.63 days vs 266.05 days) were not different between the recurrence group and nonrecurrence group. Recurrence was not related to the kind of contrast media. The recurrence rates were 23.8% (five of 21) and 27% (three of 11) when exposed to the same or different contrast agents, respectively (P = .575).

Among the 27 patients who experienced immediate hypersensitivity reactions and were reexposed to MR contrast media, 11 patients were premedicated with antihistamine or corticosteroid and four (36%) had recurrent immediate hypersensitivity reactions. Among the 16 patients without premedication, four patients (25%) experienced recurrent immediate hypersensitivity reactions. There was no difference in the recurrence rate of the immediate hypersensitivity reactions according to premedication (P = .414).

The timing of recurrence varied. While six of 27 (22%) patients experienced recurrence at their second exposure after the exposure resulting in immediate hypersensitivity reactions, two of 16 (13%) eventually experienced recurrence at their third exposure without any reaction after their second exposure after the exposure resulting in immediate hypersensitivity reactions. One of seven (14%) reexperienced immediate hypersensitivity reactions at their fourth exposure, and one of eight (13%) reexperienced immediate hypersensitivity reactions during five or more reexposures after the initial immediate hypersensitivity reaction (Fig 4).

Discussion

To our knowledge, this study involved the largest number of subjects who had gadolinium-based MR contrast media administered at a single hospital to date, and it is the first study that included detailed demographic data on the subjects.

Although the incidence of immediate hypersensitivity reactions to MR contrast media in our study was similar to the results of a previous study (0.079% vs 0.07%) (1), when the incidence per person was calculated, the rate went up to 0.121%.

Table 3

Clinical Characteristics according to Immediate Hypersensitivity Reaction Severity for the 112 Cases

Parameter	Mild Reaction	Moderate Reaction	Severe Reaction
No. of cases	93 (83.0)	8 (7.1)	11 (9.8)
Male patients*	27 (29.0)	4 (50.0)	8 (72.7)
Age (y)†	52.22 ± 15.50	40.25 ± 16.41	50.64 ± 19.28
Underlying allergic disease	8 (8.6)	2 (25.0)	2 (18.2)
White blood cell count (per microliter)†	6086.84 ± 2360.83	7905.00 ± 3330.53	5464.44 ± 1161.83
Eosinophil count (per microliter)†	140.55 ± 117.65	222.13 ± 123.02	152.56 ± 88.69
Creatinine level (mg/dL) †‡	0.876 ± 0.184	1.025 ± 0.167	1.030 ± 0.257
Estimated glomerular filtration rate†	85.72 ± 26.80	77.25 ± 15.83	80.72 ± 28.54
Use of β-blocker	2 (2.2)	0 (0)	1 (9.1)
No. of previous exposures to MR contrast media†	1.87 ± 3.07	0.63 ± 1.19	0.55 ± 0.89
Exposure history of identical contrast medium	33 (35.5)	0 (0)	3 (27.3)
Incidence of hypersensitivity reaction			
Gadoteric acid	24 (0.062)	3 (0.008)	4 (0.010)
Gadobutrol	30 (0.090)	1 (0.003)	2 (0.006)
Gadobenate dimeglumine	12 (0.189)	1 (0.016)	1 (0.016)
Gadoxetic acid	4 (0.078)	1 (0.019)	1 (0.019)
Gadopentetate dimeglumine	22 (0.052)	2 (0.005)	2 (0.005)
Gadodiamide	1 (0.006)	0 (0)	1 (0.006)

Note.—Unless otherwise indicated, data are numbers of cases, with percentages in parentheses. The severity of the immediate hypersensitivity reactions was classified into three categories following the guidelines in *ACR Manual on Contrast Media*, version 7.0 (18).

* $P < .05$.

† Data are means ± standard deviations.

‡ Patients with immediate hypersensitivity reaction at previous exposure were excluded.

Although most immediate hypersensitivity reactions were mild and urticaria was the most common symptom in our study, the incidence of moderate and severe reactions together was 0.013% per MR contrast media dose and 0.021% per person, which was rare but not low enough to be ignored.

Currently, little is known about the risk factors associated with the development of immediate hypersensitivity reactions to MR contrast agents. We reconfirmed the female predominance in immediate hypersensitivity reaction to MR contrast agents reported in previous studies (1,11) and reported the susceptibility of male patients to the severe type of immediate hypersensitivity reactions to MR contrast agents.

In prior reports, immediate hypersensitivity reactions to MR contrast media were 2.3 to 3.7 times more likely in patients with allergies or asthma (20,21). This tendency is similar to that of iodinated contrast media, where hypersensitivity reactions were reported as occurring twice as frequently in patients with allergies or asthma (22,23). In our study, the frequency of underlying allergic diseases was three times as high in the group with immediate hypersensitivity reactions compared with the group without any immediate hypersensitivity reactions.

One notable result was that the overall recurrence rate of immediate hypersensitivity reactions was as high as 30% in patients who previously experienced immediate hypersensitivity reactions, and it was remarkably higher than the general incidence rate of 0.079%. Prince et al (11) reported that patients who experienced adverse events had a higher incidence of prior reactions to gadolinium-based agents, and the American College of Radiology Committee on Drug and Contrast Media recommends that caution should be used for patients who have a history of adverse reactions after injection of MR

Table 4

Distribution of Hypersensitivity to MR Contrast Media by Severity and Sex

Parameter	Total Patients	Male Patients	Female Patients	*P* Value
No. of incidences	112/141 623 (0.079)	39/67 557 (0.058)	73/74 066 (0.098)	.006
Severity				.010
Mild	93 (83.0)	27 (69.2)	66 (90.4)	
Moderate	8 (7.1)	4 (10.3)	4 (5.5)	
Severe	11 (9.8)	8 (20.5)	3 (4.1)	

Note.—Data are numbers of cases, with percentages in parentheses.

Figure 3

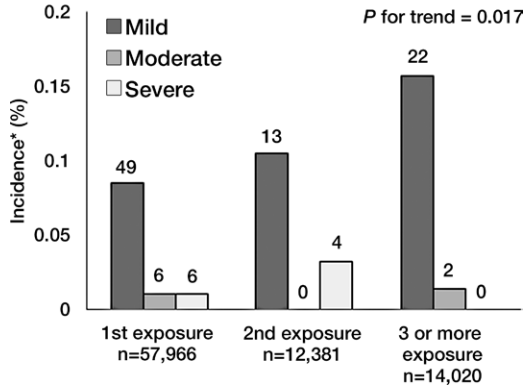

Figure 3: Graph shows incidence of immediate hypersensitivity reactions according to the number of exposures to MR contrast media and severity. The incidence of mild hypersensitivity reaction exhibited a linear trend according to the number of exposures. * = incidence of the first events of immediate hypersensitivity reactions to MR contrast media.

Figure 4

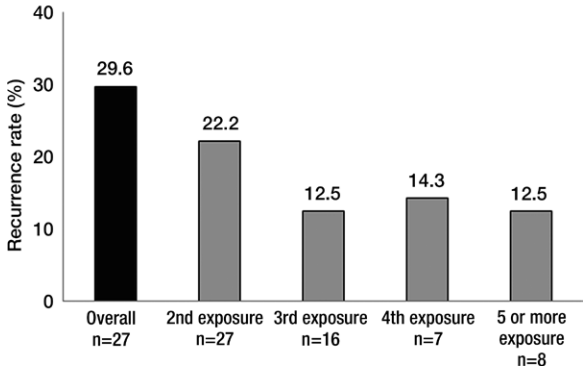

Figure 4: Graph shows recurrence rate and timing of immediate hypersensitivity reactions to gadolinium-based MR contrast media in patients with previous immediate hypersensitivity reactions. The overall recurrence rate of immediate hypersensitivity reactions to MR contrast media was 30% in patients who previously had a hypersensitivity reaction to MR contrast media.

contrast media; premedication should be administered to patients who had a previous moderate or severe reaction (18). In our study, of the 41% of patients with previous immediate hypersensitivity reactions to MR contrast media who received premedication, 64% of the patients had no subsequent immediate hypersensitivity reactions.

In our study, gadobenate dimeglumine had the highest incidence of immediate hypersensitivity reactions (0.22%), while gadodiamide had the lowest incidence (0.013%). Our results were similar to those of a recently published study (11), which reported a substantially higher adverse reaction rate to gadobenate dimeglumine and gadopentetate compared with gadodiamide. In that study, the rates of acute adverse reactions to gadobenate dimeglumine and gadodiamide were 0.12% and 0.02%, respectively (11).

We found that the mean creatinine levels were higher in patients with more severe immediate hypersensitivity reactions; however, the mean creatinine level values were within the normal range for all subgroups. Moreover, the estimated glomerular filtration rate was not significantly different according to the severity of the immediate hypersensitivity reactions. Thus, the effect of renal function on the development of immediate hypersensitivity reactions is uncertain.

We found that the rate of incidence for anaphylaxis was 0.008%, which was similar to previously reported rates of 0.004%–0.01% (9). Prince et al (11) reported a mortality rate of MR contrast material–induced anaphylaxis of 0.0019% (three of 158 796 cases), and the overall death rate reported to the U.S. Food and Drug Administration was 0.00008% from 2004 to 2009 (40 deaths per 51 million administered MR contrast material doses) (11). In our study, there was one fatality, which translated to a mortality rate of 0.0007%.

In the case of immediate hypersensitivity reactions to MR contrast media, the pathophysiologic mechanism is largely unknown. However, some reports suggest the role of an immunoglobulin E–mediated reaction in MR contrast media–related hypersensitivity (24,25). These investigators observed positive skin reactions to the MR contrast media that caused anaphylaxis. However, it is still unclear whether polysensitization and cross-reaction exist within similar molecules. Another report suggesting an immunologic mechanism revealed that the risk of immediate hypersensitivity reactions was increased up to eight times if patients had a history of hypersensitivity to MR contrast media, with the second reaction tending to be more severe than the first one (21). In our study, the overall recurrence rate after reexposure to MR contrast agent was up to 30%, and the more frequently exposed group had a higher incidence rate. To evaluate the role of the immunologic mechanism in hypersensitivity induced by MR contrast media, a skin test with MR contrast media that causes immediate hypersensitivity reactions is needed.

Our study had limitations that are associated with any retrospective study. All the medications prescribed before each MR contrast media exposure were retrieved electronically and manually reviewed to validate premedication in the group with immediate hypersensitivity reactions. This process was not performed in the group without immediate hypersensitivity reactions because of the difficulty involved and the low likelihood of premedication being routinely prescribed for MR contrast media in practice. Instead of a thorough review for premedication, we

screened the medical records of 500 randomly selected subjects from the group without immediate hypersensitivity reactions, and no one was premedicated before the administration of MR contrast media. Therefore, the possibility of underestimation of the immediate hypersensitivity reaction because of premedication seems to be very low. Another limitation was that the doses of gadolinium-based MR contrast media given to each patient were not clearly defined. In addition, information on exposure to MR contrast media before January 2000 was not complete, and exposures at other institutions were not obtained.

For more precise analyses on the clinical features and pathogenic mechanisms related to MR contrast media–induced immediate hypersensitivity reactions, large-scale prospective studies including in vivo and in vitro allergy tests are needed.

In summary, in our study, MR contrast media induced immediate hypersensitivity reactions at an incidence rate of 0.079%. The risk factors for immediate hypersensitivity reactions include the female sex, underlying allergic diseases, multiple exposures, and a previous history of hypersensitivity to MR contrast media. The recurrence rate of immediate hypersensitivity reactions was 30% in patients who previously experienced hypersensitivity reactions. Therefore, premedication should be considered for patients who had previous immediate hypersensitivity reactions.

Disclosures of Potential Conflicts of Interest: J.W.J. No potential conflicts of interest to disclose. **H.R.K.** No potential conflicts of interest to disclose. **M.H.K.** No potential conflicts of interest to disclose. **W.L.** No potential conflicts of interest to disclose. **K.U.M.** No potential conflicts of interest to disclose. **M.H.H.** No potential conflicts of interest to disclose. **S.H.C.** No potential conflicts of interest to disclose.

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