Case Report

Demonstration of an IgE-Mediated Immunological Pathogenesis of a Severe Adverse Reaction to Gadopentetate Dimeglumine

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Summary: In this case report, the authors, after reviewing the literature data about contrast agents in Magnetic Resonance Imaging (MRI) and correlated problems, investigate the immunological mechanism of an adverse reaction to gadopentetate dimeglumine (Gd-DTPA), in order to demonstrate an IgE-mediated immunological pathogenesis. The case of a patient who underwent MR imaging in our hospital was studied. During, and after, the MR examination with Gd-DTPA the patient showed local warmth/pain to the external genitalia and to the face, tachycardia, nausea, vomiting, diarrhea, uterine cramps, and diffuse cutaneous rash. Skin tests (intradermal) and the passive transfer test according to Prausnitz and Küstner were positive, suggesting the involvement of an I-type allergy (IgE-mediated) mechanism. In this paper, we demonstrate that the adverse reactions to Gd-DTPA can be supported by an immunological mechanism.

Keywords: allergy, contrast media, gadolinium, adverse drug reaction

Introduction

Gadolinium-based contrast agents are used routinely for magnetic resonance imaging (MRI). Gadopentetate dimeglumine (Gd-DTPA) is one of the most commonly used MRI contrast agents; it is an acyclic chelate complex, which has an osmolarity of 1.96 Osm/kg water at 37° C. It is excreted by glomerular filtration (83% within 6 hours); minimal excretion occurs via the gastrointestinal tract [1]. Gd-DTPA is also a very poor activator of the complement system, which is thought to play a role in the induction of anaphylactoid reactions.

The incidence of adverse reactions to gadolinium-based contrast agents ranges from 0.06% to 15%; the reactions include headache, nausea, vomiting, hypotension, urticaria, cutaneous rash, and anaphylactic shock [2–5].

The incidence-rate of adverse reactions is increased in subjects with clinical signs and symptoms of bronchial asthma or allergy, and in subjects with previous adverse reactions to iodinated contrast agents or to gadolinium-based contrast agents [4].

Serious adverse reactions such as anaphylactic shock, edema of the glottis, and death have also been described after the injection of Gd-DTPA [5–8]. The relationship between such deaths and the injection of Gd-DTPA has not been completely clarified. In the literature, adverse reactions to Gd-DTPA with an immuno-allergic etiology (with positive allergological tests) are not reported, since in the described cases no allergological examinations have been performed.

Case Report

We report the case of a 29 year-old woman who underwent a MR examination for the first time with intravenous

Table 1. Results of the allergological tests.

Skin tests	Method	Dilution	Patient results	Control group results (10 healthy subjects)
Gadopentetate dimeglumine	Prick	1:10000	Negative	Negative
		1:1000	Negative	Negative
		1:100	Negative	Negative
	Intradermal	1:10000	Negative	Negative
		1:1000	Negative	Negative
		1:100	Positive	Negative
	Patch	Pure solution	Negative	Negative
	Prausnitz-Küstner test	1:1000	Both parents negative	
		1:100	Positive in one parent	
		1:10	Both parents positive	
	Inactivated serum Prausnitz-Küstner test	1:1000	Negative	
		1:100	Negative	
		1:10	Negative	
Iodamide, Iohexole, Iopamidole, Amidotrizoic-Dimeglumine, Iopromide	Intradermal	1:10.000	Negative	Negative
		1:1000	Negative	Negative
		1:100	Negative	Negative
	Patch	Pure solution	Negative	Negative

infusion of Gd-DTPA (Magnevist, Bracco) in January 1994, without any problem. In July 1999, the patient repeated the MR examination and complained of local heat to the external genitalia and to the face, tachycardia, nausea, vomiting, diarrhea, uterine cramps, and diffuse cutaneous rash during the administration of the contrast agent. For these reasons, the patient received betamethasone and teophyllin, with benefit. After being admitted in our Department, the patient underwent skin tests (prick and intradermal) with Gd-DTPA (Magnevist, Bracco). We used 1/10,000, 1/1000 and 1/100 diluted solutions. Negative (saline) and positive (10 mg/ml histamine) controls were also performed. With the intradermal injection of 1/100 diluted solution, the patient showed an evident wheal and flare reaction at the site of the injection (Table 1).

The intradermal test with the same concentration on ten healthy control subjects, who had no history of allergic reactions, resulted negative. Patch tests carried out with Gd-DTPA were negative. Skin tests carried out with other contrast agents, such as iodamide (Uromiro, Bracco), iohexole (Omnipaque, Bracco), iopamidole (Iopamiro, Bracco), amidotrizoic dimeglumine (Selectografin, Bracco), and iopromide (Ultravist, Bracco) all resulted negative (Table 1). After the test for HIV, B Hepatitis, and C Hepatitis had negative results; a passive transfer test according to Prausnitz and Küstner was carried out on the patient's parents, with the intradermal injection of patient's serum on the two receptors localized on their forearms. Informed consent by the patient's parents and a favorable opinion by the hospital ethics committee were first obtained. Three intradermal injections with 0.10 ml of serum were performed in each receptor. After 48 h, 0.05 ml of 1:1000, 1:100, and 1:10 diluted solution of Gd-DTPA were injected in the same point, and after 20 min the reaction was evaluated. This was positive in one with the dilution 1:10, and in the other with the dilution 1:10 and 1:100. The test, repeated with the serum held to the temperature of 56° C for 3 h, resulted negative, showing in an incontestable way the presence of specific direct IgE against the Gd-DTPA.

Discussion

Many authors [9] support the thesis that adverse reactions after the administration of iodinated contrast agents, or of those containing gadolinium, are correlated to the ratio

between osmolarity and injected volume, which would determine a direct liberation of chemical mediators from mast cells.

This would explain the major incidence of adverse reactions observed after the use of iodinated substances, compared to those observed after the use of substances containing gadolinium. This could be due to a greater volume (around 10 times) used in the former.

However, some authors think that this is not the sole etiopathogenetic mechanism implicated [10].

Several studies have confirmed the relative safety of Gd-DTPA in the general population, even if the incidence of adverse reactions becomes significant in subjects with a positive history for allergy or bronchial asthma and, especially, with previous adverse reactions to iodinated contrast agents or to contrast agents containing gadolinium [4].

In this paper, we have shown, for the first time, that adverse reactions after administration of Gd-DTPA can also be supported by an immunological mechanism.

The positivity of the skin tests indicate a first type (IgE-mediated) allergy, which is well correlated with the absence of adverse reactions after the first MR test with infusion of Gd-DTPA. This step evidently represented the phase of sensitization, which was confirmed unequivocally with the passive transfer test according to Prausnitz and Küstner.

On this basis, we recommend that allergological tests be performed on subjects at risk (i.e. with previous reactions with iodinated contrast media or MRI contrast agents). In patients with positive skin tests, it would be advisable to choose other kinds of contrast agents, or to consider the possibility of a specific desensitizing treatment [11]; in patients with a negative allergological examination, the administration of an anti-reactive therapy with steroids and anti-histamine drugs may be suggested.

This case of IgE-mediated adverse reaction to Gd-DTPA, is, to our knowledge, the first one described in literature.

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