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Clinical value of negative skin tests to gadolinium contrast agents

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Magnetic resonance imaging (MRI) contrast agents are classically considered to be safe, although anaphylactic reactions have been reported (1). To date, few detailed reports incriminating an IgE-dependent mechanism related to the use of these agents have been published (2–4).

We present the gadolinium contrast agents (GdAs) skin test (ST) results of all consecutive patients who were referred to our allergy department over the last 5 years with a compatible clinical history of GdA hypersensitivity and who were re-challenged after negative STs.

Before performing STs, clinical data were registered using the EAACI-ENDA drug allergy questionnaire (5). The severity of the initial reactions was assessed according to the Ring and Messmer (6) classification (localized reactions will be further referred to as grade 0 reactions). Skin tests were performed in accordance with EAACI-ENDA. Skin prick tests (SPTs) were performed with an undiluted MRI con-

trast agent and, when negative, were followed by intra-dermal tests (IDT) in the range of 10^{-3} to the 10^{-1} dilution of the commercially available contrast media, which, in our experience, proved to be a nonirritant threshold (4). Patients with negative STs (either the suspected GdA or an alternative GdA in the case of a positive ST for the suspected GdA) were contacted and asked standard questions about whether or not they had undergone another gadolinium administration after the allergy work-up and what the outcome was.

From January 2006 to April 2011, STs to GdAs were performed on 27 patients. The severity of the reactions was as follows: 37.0% grade 0 and I, 33.3% grade II, and 14.8% grade III. Three patients (11.1%) presented an isolated bronchospasm and 1 (3.8%) reported a nonimmediate reaction. An

immunological mechanism – as documented by positive immediate IDTs – accounted for five cases, three grade III and two grade II reactions, respectively. According to our protocol on GdA hypersensitivity diagnostic procedure, negatively skin-tested GdAs were authorized for future MRIs.

All 27 patients were contacted (100% participation rate), either directly or through their attending physician, after a median time interval since allergy work-up of 26.9 (1–63) months. When asked about subsequent administration of GdA, 12 patients (44.4%) reported lack of indication for a new MRI. In four cases (14.8%), MRI without contrast was preferred.

Eleven patients (40.7%) underwent a new injected MRI (Fig. 1) and, when re-exposed, they all tolerated the negatively skin-tested GdA without reaction

'The negative predictive value of gadolinium skin tests seems to be of value.'

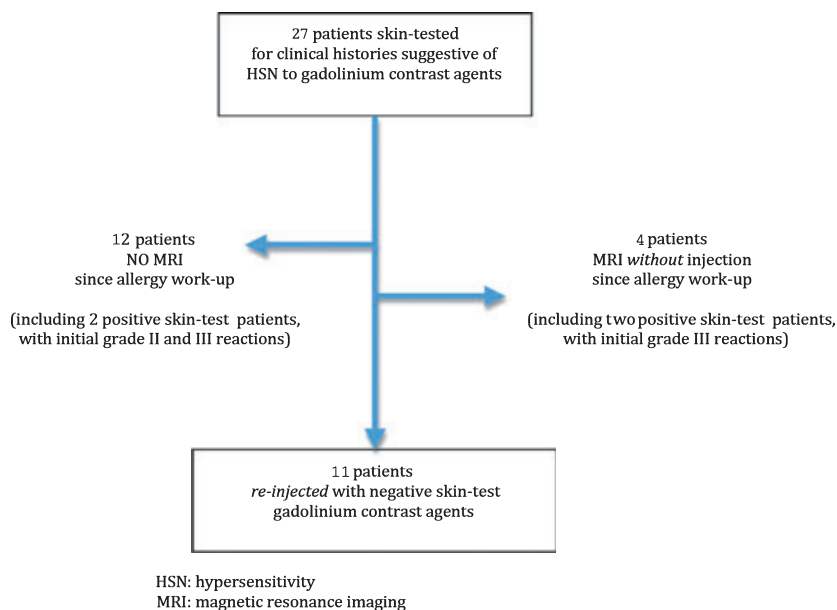


Figure 1 Flow chart of 27 patients tested for suspected GdA hypersensitivity.

Table 1 Patients' characteristics

Patient #	Age	Sex	Type of exam	Name of culprit GdA	Initial reaction	Grade of initial reaction	Delay (months)*	Skin-tests	Delay (months)†	Premedication	GdA re-injected	Side effects
1	71	F	NS	Prohance®	Pruritus, dyspnea	Immediate II	4	Negative	NS	NS	Prohance®	None
2	43	F	NS	NS	Urticaria, angioedema	Immediate 0/II	35	Negative	NS	NS	Magnevist®	None
9	58	F	Cerebral MRI	MultiHance®	Urticaria	Immediate 0/II	1	Negative	2	None	MultiHance®	None
12	65	F	Breast MRI	Prohance®	Urticaria	Non-Immediate mild	2	Negative	23	antiH1, GCS	Dotarem®	None
14‡	42	M	Liver MRI	NS	Maculopapular exanthema	Immediate 0	36	Negative	NS	NS	Magnevist®	None
17	48	F	NS	Prohance®	Angioedema	Immediate 0	4	Negative	NS	NS	Prohance®	None
22	60	F	Breast MRI	NS	Dyspnea, cough	Immediate isolated BHR	60	Negative	NS	NS	Magnevist®	None
23	58	F	NS	Prohance®	Urticaria, dysphagia	Immediate I	72	Negative	5	None	Prohance®	None
25	55	F	Cerebral MRI	NS	Facial erythema	Immediate 0	18	Negative	2	None	Dotarem®	None
26§	27	F	Cerebral MRI	NS	Angioedema, dyspnea, hypotension	Immediate III	95	Negative	1	antiH1	Dotarem®	None
27	37	F	Cerebral MRI	MultiHance®	Urticaria, dyspnea, abdominal cramps	Immediate II	2	Positive¶	6	antiH1	Dotarem®	None

*Delay between reaction and skin tests.

†Delay between skin tests and new RCM injection.

‡Patient no 14 presented 2 similar episodes, 1 year apart.

§Patient no 26 presented an identical reaction after iodinated RCM (negative skin tests); she suffered from hypothyroidism and was treated with Levothyrox; premедication with antihistamines with authorised for future radiocontrast media injections.

¶Immediate positive IDT for MultiHance.

BHR: bronchial hyperresponsiveness; GdA: gadolinium contrast agent; F: female; M: male; NS: not specified; antiH1: antihistamines; GCS: glucocorticoids; MRI: magnetic resonance imaging; IDT: intradermal testing; RCM: radiocontrast media; Prohance®: Gadoteridol Gd-HP-DO3A; MultiHance®: Gadobenate dimeglumine Gd-BOPTA; Magnevist®: Gadobenate dimeglumine Gd-DTPA; Dotarem®: Gadoterate meglumine, Gd-DOTA.

(Table 1). The median delay between the STs and the new radiocontrast media (RCM) injection was 6 months (1–23). Data regarding premедication were available in six patients (Table 1).

The excellent negative predictive value of skin testing in our series is obviously biased by the small sample size and the mild severity of the initial reactions.

Nevertheless, these data allow certain conclusions to be drawn. The patients with severe reactions (#26, with a prior grade III nonIgE-mediated anaphylaxis and #27 with grade II IgE-mediated anaphylaxis) were administered and tolerated a negatively skin-tested GdA. This is in accordance with the reports of others (3), and it underlines the importance of an accurate allergy assessment, principally STs, to document the drug's involvement and to search for alternatives.

Conclusive evidence on the value of STs in GdA hypersensitivity cannot be inferred on the basis of the scarce cases of positive STs reported in the current literature, because these patients have not been re-injected with the positive ST GdA.

This explorative study is consistent with the ongoing approach in drug allergy work-up, and according to our limited population, the negative predictive value of gadolinium STs appears to be of interest. Further studies should confirm these results.

The authors have no conflict of interest for this study.

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