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Hypersensitivity reactions to iodinated contrast media in Italy: a retrospective study. Characteristics of patients and risk factors

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Key words

Iodinated contrast media; risk factors; drug hypersensitivity; drug immediate reactions; drug delayed reactions.

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Impact statement

Characteristics of patients with hypersensitivity reactions to iodinated contrast media are described and compared with subject tolerating the same contrast media allowing to identify some possible risk factors.

Summary

Objective. *The purpose of the study was to describe the characteristics of patients experiencing hypersensitivity reactions (HRs) to iodinated contrast media (ICM) in a large Italian population and to investigate potential risks factors in order to obtain a risk stratification, helpful in the management of these patients.* ***Methods****. Data of 407 patients investigated in 9 Italian Allergy Centers for suspected HRs to ICM were analyzed and compared with a control group of 152 subjects that tolerated one or more ICM-enhanced examinations. The univariate and multivariate logistic regression model was used to evaluate associated factors.* ***Results.*** *The mean age of reactive patients was 61 years and 60% were female; 67% of patients reported immediate reactions and 35% experienced the reaction, more frequently with immediate onset, at the first examination in life. Iomeprol, iopromide and iodixanol were the most frequent culprit agents and 20% of patients showed a positive skin test result. Previous adverse reactions to ICM were reported by 15.6% of patients. The multivariate analysis showed that male gender and age > 65 were associated with ICM reactions as protective factors [OR_{adja} = 0.51; 95% CI 0.33-0.77 and OR_{adja} = 0.60; 95% CI 0.39-0.92 respectively]. Cardio-vascular disease [OR_{adja} = 2.06; 95% CI 1.22-3.50)], respiratory allergy [OR_{adja} = 2.30; 95% CI 1.09-4.83)] and adverse drug reactions [OR_{adja} = 1.99; 95% CI 1.05-3.77)] were identified as risk factors for ICM reactions. Food allergy was not significantly associated with reactions [OR_{adja} = 1.51; 5% CI 0.41-5.56].* ***Conclusions.*** *This is the largest study on Italian patients experiencing hypersensitivity reactions to ICM. Most results are in line with other studies, showing some association with factors that could influence the incidence of hypersensitivity reactions but not allowing an easy risk stratification.*

Introduction

The introduction and increasing use of nonionic low-molecular-weight (LMW) iodinated contrast media (ICM) have significantly reduced the risk of adverse reactions related to contrast-enhanced radiologic imaging. Hypersensitivity reactions (HRs) to ICM are rare, but their potential severity represents a cause of concern both for radiologists and for people who need contrast-enhanced radiologic examinations.

This could explain the growing interest in the topic in the last 15 years, not only by radiologists but also by allergists who can give a contribution to knowledge, comprehension and consequently a more correct approach to these reactions (1-4). For this purpose, the European Network of Drug Allergy (ENDA) published in 2009 the results of a prospective multicenter study aimed to investigate clinical aspects and a potential allergy work-up in this field (5). Although some areas still remain controversial, as outlined in a recent international consensus, this new perspective has stimulated the interest to deepen various aspects of the problem (6). Among them, the identification of patients at risk of reaction and the real utility of the pharmacological premedication are particularly intriguing. The consensus well resumes the hypothetical risk factors based on the existing studies: while a previous reaction to contrast media is generally accepted as the main risk factor, the current role of other conditions, such as atopy, asthma, cardiovascular diseases, drug allergy, female gender, mastocytosis, repeated administrations of ICM, *etc*., is still uncertain. Nevertheless, these conditions are often considered in clinical practice, arising fear both in patients and operators. One of the practical consequences is the abuse of pharmacological premedication by antihistamines and steroids, without standardized regimes and with differences not only between allergists and radiologists, but also between the North American and European recommendations (7, 8).

To the best of our knowledge, there is no Italian national multicenter study on hypersensitivity reactions to ICM. Therefore, the main purpose of this study was to investigate the characteristics of patients referred to allergy evaluation for suspected hypersensitivity reactions to ICM in different Allergy Centers in Italy. The secondary aim was to analyze possible association between some factors and hypersensitivity reactions to ICM, with the purpose to identify the possibility of a risk stratification, a particularly useful tool in adverse drug reactions (ADRs) evaluation (9).

Methods

This is a retrospective multicenter study approved by the Ethics Committee of the coordinating Center (L'Aquila and Teramo provinces, Avezzano Hospital - 1/CE/17).

Patients

From 2013 to 2016, in nine Italian Allergy Centers with expertise in drug allergy management, 407 consecutive patients with hypersensitivity reactions to ICM were analyzed as "reactive group". Data of 152 consecutive patients from three Italian Radiologic Centers were collected as "control group" because they tolerated one or more contrast-enhanced examinations.

The following demographic and clinical data were recorded: age, sex, radiological examination, administered ICM, history of previous exposures, number of examinations in the last year, use of premedication, history of allergy (inhalant or food allergy) and/or ADRs other than ICM, concomitant cardiovascular diseases, usual anti-hypertensive medications (*i.e*., angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers). In the reactive group, the characteristics of the last ad-

verse reaction and the history of previous ICM reactions, bronchial asthma, angioedema or mastocytosis were also considered.

Clinical symptoms

In the reactive group, clinical symptom onset was classified in immediate (< 1 hour) and non-immediate (> 1 hour). Moreover, the reaction delay was further specified, in order to differentiate very rapid (< 10 minutes) and very delayed (> 48 hours) reactions. These data were correlated with the severity of the reaction. Immediate hypersensitivity reactions (IHRs) were classified according to the Ring and Messmer severity scale: grade I indicating only cutaneous and/or mucosal symptoms, grade II indicating moderate multiorgan involvement with cutaneous and respiratory or gastrointestinal and/or cardiovascular symptoms, grade III including severe life-threatening multiorgan involvement such as cardiovascular collapse, arrhythmias and bronchospasm, grade IV with the cardiac and/or respiratory arrest (10). The non-immediate hypersensitivity reactions (NIHRs) were classified according to the ENDA study in mild, moderate, and severe (5).

Skin tests

As a part of the routine allergy workup, skin tests for the culprit ICM (when known) and for others ICMs commonly used in Italy were performed in 400 patients. In accordance with the ENDA criteria (5), patients with history of IHR were analyzed with skin prick test (SPT) and, if negative, with intradermal test (IDT). Patients with clinical history of NIHR underwent patch test (PT) with reading until 96 hours and, if negative, SPT and IDT. Reactivity to IDT was evaluated after 20 minutes and during the following 48 hours to detect delayed reactions.

Statistical analysis

Continuous variables were expressed as mean and standard deviation, and categorical variables as numbers and percentages. Data were compared using Student's t- or chi-square tests depending on scale level and distribution.

To evaluate factors related to hypersensitivity reactions to ICM, subjects in the reactive group were compared with subjects in the control group. A logistic regression model was used for univariate analysis with reaction to ICM (yes/no) as dependent variable and the following factors as independent factors: gender, age in years (≤ 65; > 65), first exposure to ICM (yes/no), number of examinations in the last year, premedication (yes/no), cardiovascular disease (yes/no), number of concomitant pathologies (classes: 0; 1-2; ≥ 3), respiratory allergy (yes/no), food allergy (yes/no), adverse drug reactions (yes/no) and anti-hypertensive medications such as ACE-inhibitors (yes/no), and angiotensin receptors blockers (yes/no).

All factors statistically significant by univariate model were included in a multivariate logistic regression analysis (MLRA). Unadjusted odds ratios (ORs) and adjusted odds ratios (OR_{adj}) with 95% CIs were reported. Significance was assumed for $p < 0.05$. All analysis was performed using STATA 14 software.

Results

Characteristics of patients in the reactive group (see **table I**)

A total of 274 patients reported IHR (67%: 95% CI 63%-72%), whereas 133 patients reported NIHR (33%: 95% CI 28%-37%), 164 patients were males (40%) and the mean age was 61 (± 14.5) years. Eighty-five percent of them were diagnosed with ICM reactions after a computed tomography (CT) scanning.

Premedication had been administered before the radiological examination in 78 patients (19% out of 407) who showed significantly more frequently a non-immediate rather than an immediate reaction. Among 54 patients with previous adverse reactions, 42 were premedicated.

One hundred twenty-four patients (35% of 351 − because of missing data) experienced the reaction during the first ICM-enhanced examination in their life and significantly more frequently with an immediate rather than delayed onset.

Previous reactions to ICM were reported by 54 patients out of 351 (15.4%), without any difference between IHR and NIHR. Although the suspected culprit agent was known only in about 60% of cases, among the various ICM, iomeprol and iopromide were involved in over 50% of the known cases without significant difference between IHR and NIHR. Moreover, iomeprol was frequently the culprit agent of severe immediate reactions (degree 3 and 4), whereas iodixanol was responsible significantly more frequently in nonimmediate reactions (16% NIHR *vs* 3% IHR; $p < 0.001$). In the reactive group, 81 patients reported a history of respiratory and/or food allergy and 86 patients presented previous ADR to drugs other than ICM. Among patients with respiratory allergy only 26 (36.6%) reported bronchial asthma.

A history of angioedema was present in 2 patients, no cases of mastocytosis were registered.

Severity and time to onset of reaction

The grade of severity of immediate reactions was classified as follows: grade I in 142 (52%) patients, grade II in 80 (29%) patients, grade III in 41 (15%) patients and grade IV in 11 (4%) patients. NIHR were mostly mild (61%) and only one patient reported a severe nonimmediate reaction diagnosed as DRESS syndrome.

Forty-six per cent of immediate reactions (126/271) occurred within ten minutes, and the same rate within 30 minutes. Among the non-immediate reactive group, the reactions were mostly registered within 24 hours (97/130). Only 8.5% of patients reported reactions over 48 hours after the examination.

Figure 1 shows the relation between time of reactions and severity. More than half of immediate severe reactions happened within 10 minutes from the ICM injection.

Table I *- Characteristics of patients in the reactive group (n = 407).*

	IHR n = 274 [67%: 95% CI 63%-72%]	**NIHR n = 133 [33%: 95% CI 28%-37%]**	
	n (%)	n (%)	p**
Gender			
Female	156 (57)	87 (65)	0.102
Age (years)	60.7 (± 14.4)	62.5 (± 14.9)	0.245
Pre-medication (yes)	44 (16.3)	34 (26.15)	0.020
First examination (yes)	91 (39)	33 (28)	0.052
Previous reactions	34 (14.2)	20 (18.9)	
Exam type			
C.T. scan	233 (85.04)	113 (84.96)	0.563
Coronarography	17 (6.20)	13 (9.77)	0.196
Urography/cholangiography	18 (6.57)	1 (0.75)	0.010
Other	5 (1.82)	6 (4.51)	0.400
Implicated contrast medium			
Iomeprol	53 (19.34)	21 (15.79)	0.383
Iopromide	34 (12.41)	26 (19.55)	0.057
Iobitridol	23 (8.39)	7 (5.26)	0.315
Iopamidol	18 (6.57)	4 (3.01)	0.165
Iodixanol	9 (3.28)	21 (15.79)	< 0.001
Iohexol	5 (1.82)	3 (2.26)	0.720
Ioversol	14 (5.11)	9 (6.77)	0.497
Unknown	118 (43.07)	42 (31.58)	0.026
History of allergy	96 (35.04)	54 (40.60)	0.275
Respiratory	49 (18.08)	22 (17.05)	0.802
Food	18 (6.64)	7 (5.43)	0.639
Adverse drug reactions	52 (19.19)	34 (26.56)	0.188

**Chi Square/Fisher exact test.

Skin tests

Allergy workup demonstrated at least one positive skin test in 81 patients (20.25% of total enrolled patients): 42 patients were in the IHR group, representing the 15.7% of them, and 39 patients were in the NIHR group, accounting for the 29.3%. Among patients with history of reaction at their first exposure, 21% showed a positive test.

A more detailed description of the results will be the subject of a subsequent paper.

Factors related to ICM reactions (see **table II**)

In order to evaluate potential risk factors related to ICM hypersensitivity reactions, data of 152 subjects that underwent an ICM − enhanced CT − scan without any adverse reaction were collected as control group and analyzed.

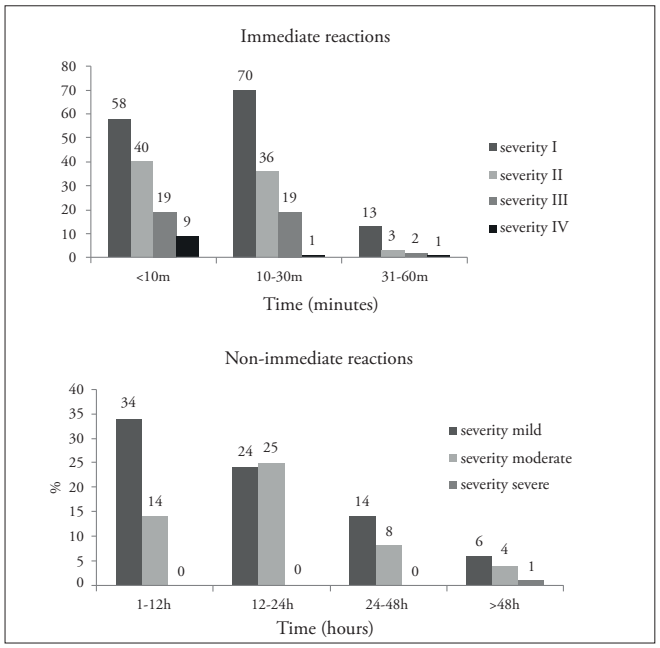
The ICMs used in the control group were the same as in the reactive group (iopamidol in 40%, iomeprol in 32%, iobitridol in 15%, iohexol in 9%, iodixanol in 4%) with the exception of iopromide and ioversol, never used in the control group.

Collectively, 176 patients reported history of at least one allergy (food allergy, respiratory allergy) and/or ADRs; 150 patients were in the reactive group (37%: 95% CI 32%-42%) whereas only 26 patients were in the control group (18%: 95% CI 12%-26%).

Univariate analysis between reactive and control group showed a significant association with the following factors: first exposure (OR = 2.2), cardio-vascular diseases (OR = 2.1), history of allergy (respiratory: OR = 3.0; food: OR =3 .3) or ADR (OR = 2.5). Male gender and age > 65 years were protective factors against reactions.

The multivariate analysis showed that food allergy was not a significant risk factor associated with reactions: OR_{adj}= 1.47 (95% CI 0.40-5.41), while female gender, age ≤ 65 years, first ICM exposure, associated cardio-vascular disease, a history of respiratory allergy and adverse drug reactions were significant risk factors for ICM hypersensitivity reactions (**table III**).

Figure 1 *- Time to onset of immediate and non-immediate reactions by severity.*



Not 407 because of missing data.

Discussion

This is the first Italian multicenter study aimed to analyze characteristics and risk factors of patients evaluated for suspected hypersensitivity reactions to ICM. Demographic characteristics were similar to those of the European multicenter study (5), with a larger sample size (407 *vs* 240) and to those of 98 patients in a recent Italian study (11).

Thirty-five percent of patients were on their first exposure, showing more frequently an immediate reaction. The possibility of hypersensitivity reactions to ICM, both immediate and non-immediate, in patients previously unexposed was already observed, ranging from 13.4% to 50% (5, 11-15). It is usually attributed to a non-immunological mechanism of action, but some cases show positive skin test with a variable prevalence (35% in ENDA study and 21% in our study). This seems to suggest a possible previous sensitization through unknown environmental molecules, or molecules containing carbamoyl side chains (14), or ICM-contaminated drinking water (16).

The use of pharmacological premedication was less frequent than expected: specifically, premedication treatment with either steroids and/or anti-histamines was administered in the majority of cases with a history of previous reactions but not in the totality of them. The reason why these patients showed more frequently non-immediate reactions is not clear. One hypotesis is that premedication could be not adequate to prevent late reactions.

In our study, the rate of patients with at least one positive skin test (20.25%) is lower than that reported in some studies (5, 12, 14) but higher in comparison with others (11, 13), confirming the role of allergy workup in diagnosing and discriminating between cases with immunological and non-immunological pathogenesis. The time interval between reaction and evaluation is an important factor influencing the results and could be the reason for the significant more frequent positivity of test in patients with non-immediate hypersensitivity reactions, less influenced by this factor.

Of note, only 16% of our reactive group reported one or more previous ICM adverse reactions. This is described as the most important risk factor for ICM hypersensitivity reactions, with a variable frequency from 13 to 26 % (5, 12). In a recent study the incidence of HRs was about 20 times higher in patients with a previous history of ICM reactions than in those without (17).

The secondary aim of our study was to evaluate also the role of other potential risk factors related to ICM hypersensitivity, in order to obtain a risk stratification that may enable a "delabelling" of low-risk subjects, focusing attention on high-risk subjects. Literature is rich but inconclusive and sometimes contradictory on this topic (15-19). Our analysis confirmed the results of other studies about higher risk in female sex (20, 21), age < 65 years and a more frequent association with cardiovascular diseases (22, 23) in the reactive group.

Regardless of his endotype, bronchial asthma is often included in the list of risk factors for ICM HRs with an important difference in the strength of association (OR 2.0-OR 8.74) (18, 19, 21). In our study population, the small number of patients with bronchial asthma did not allow us to correctly analyze this topic. Probably, only uncontrolled asthma has to be considered a risk factor because it may increase the severity of HR. Such patients are often poor candidates for receiving contrast, and it is usually avoided by the treating radiologist (24).

In line with other studies reporting a prevalence of atopy ranging from 29 up to 50% (5, 11-13), in our reactive group history of allergy and/or ADRs was present in 37% [95% CI: 32%-42%]. Inhalant allergy (but not asthma) and ADRs resulted significantly associated with ICM HRs, whereas food allergy was not significantly associated. In literature, history of concomitant allergy or atopy, with or without a specific disease, is often mentioned as a risk factor, even in recent studies, reviews, and guidelines (6, 9, 18, 25). The importance of this association should be reduced considering that this concept seems passively transferred from one review to another, while observational studies usually report only anamnestic data, not confirmed by diagnostic tests. This is also true for our study where the level of statistical significance of these results is very low. At the end, this

Table II *- Factors related to ICM reactions.*

		Reactive group N = 407	**Control group N = 152**			
		n (%)	n (%)	p*	OR**	95% CI
Gender	Female	243 (60%)	67 (44%)	< 0.01	Rif	
	Male	164 (40%)	85 (56%)		0.5	0.4-0.8
Age (years)	< 65	208 (51%)	58 (39%)	< 0.01	Rif	
	≥ 65	198 (49%)	89 (61%)		0.6	0.4-0.9
First exposure				< 0.01	Rif	
	Yes	124 (35%)	29 (20%)		2.2	1.4-3.5
Pre-medication	Yes	78 (20%)	20 (14%)	0.141	Rif	0.9-2.5
					1.5	
Number of examinations in the last year	0	193 (60%)	21 (31%)	< 0.01	Rif	
	1-2	112 (35%)	15 (22%)		0.8	0.4-1.6
	≥ 3	17 (5%)	32 (47%)		0.0	0.0-0.1
Cardio-vascular disease				< 0.01	Rif	
	Yes	120 (29%)	25 (16%)		2.1	1.3-3.4
Respiratory allergy				< 0.01	Rif	
	Yes	71 (18%)	10 (7%)		3.0	1.5-6.0
Food allergy				0.049	Rif	
	Yes	25 (6 %)	3 (2 %)		3.3	1.0-0.9
Adverse Drug reactions				< .001	Rif	
	Yes	86 (22%)	15 (10 %)		2.5	1.4-2.6
ACE-inhibitors				0.249	Rif	
	Yes	54 (15%)	15 (11 %)		1.4	0.8-2.6
Angiothensin receptor blockers				0.352	Rif	
	Yes	35 (10%)	4 (7 %)		1.4	0.5-4.2

*Chi Square test; **univariate logistic model. The numbers within the categories do not have the total of 559 due to missing data.

Table III *- Factors associated to reactions (multivariate analysis).*

		OR	**p**	**95% CI**
Gender	Female	Rif		
	Male	0.51	0.002	0.33-0.77
Age (years)	< 65	Rif		
	≥ 65	0.60	0.020	0.39-0.92
First exposure	No	Rif		
	Yes	2.84	0.005	1.24-3.30
Cardio-vascular disease	No	Rif		
	Yes	2.06	0.007	1.22-3.50
Respiratory allergy	No	Rif		
	Yes	2.30	0.027	1.09-4.83
Food allergy	No	Rif		
	Yes	1.47	0.560	0.40-5.42
Adverse drug reactions	No	Rif		
	Yes	1.99	0.034	1.05-3.77

could suggest only a generic predisposing role of other allergic conditions towards hypersensitivity reactions to ICM.
We did not find a significant difference about some factors often reported as a cause of increased risk or increased severity of anaphylactic reactions such as use of some antihypertensive drugs (21, 26) and history of angioedema or mastocytosis (18), due to the rarity of cases in our study population.
Considering the variables related to the examination, in our study a significant difference between reactor and control subjects seems to indicate that the first exposure of life may represent a risk of reaction. Hypothesis confirmed in the multivariate analysis and discussed above. Conversely, the number of previous ICM examinations or their frequency is sometimes indicated among risk factors (18, 25). Of note, in our study the number of examinations in the last year before the reaction was significantly greater in the control group compared to the reactive one, probably due to the high number of oncologic patients, more frequently exposed to ICM-enhanced examinations. This result seems to confirm the hypothesis of a lower risk in subjects not susceptible who did not react at the first examination (27).
A recent Italian document about the management of patients at risk of HRs to contrast media proposes a classification in which only patients with associated active pathologies such as urticaria-angioedema, mastocytosis, uncontrolled asthma, history of idiopathic anaphylaxis, and patients with previous reactions to ICMs regardless of their severity, are considered at increased risk (28). All the other discussed risk factors are considered irrelevant. The future practical use of these guidelines is needed to confirm whether this is the right way to manage these patients.

Conclusions

This is a multicenter retrospective study on 407 patients evaluated for suspected hypersensitivity reactions to iodinated contrast media. Characteristics of patients and reactions are in line with other studies coming from different countries. One of the aims of the study was the evaluation of possible risk factors associated with HRs to ICM in order to obtain a risk stratification of patients. In summary, our data seem to suggest that these reactions could be the result of multiple factors acting together with different association in predisposed subjects: age, sex, allergic diseases, cardiovascular diseases, previous reactions to these agents and features of the contrast examination. This may be the reason for contradictory results in the literature and for the difficulty in obtaining a valid risk stratification. Among these factors, our study confirms the risk of reaction, mostly immediate and also with the possibility of severe anaphylaxis, in patients at their first contrast examination (35% of patients in this study): it deserves great attention among radiologists and others who administer these drugs. Future research will better clarify the mechanisms and may suggest some corrective action, for example, to reduce the ICM environmental contamination and consequent sensitization of general population (29). This study, of course, presents some limitations. First of all, the retrospective design limiting the interpretation of the results. In fact, the study may be affected by selection and detection bias and the lack of possible investigations about some concerns. The lack of some data represents a further limitation. Nevertheless, until now, it represents the largest study on patients with ICM hypersensitivity reactions in Italy. A prospective observational study would better assess various investigated or not investigated aspects of the topic.

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Conflict of interests

The authors declare that they have no conflict of interests.

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