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Allergy to the iodinated contrast media – the clinical and immunological aspects – a literature review

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ABSTRACT

Aim. The aim of this paper is to analyse and review the currently available evidence and research with regard to allergy to the iodinated contrast media, which still remains an important, albeit rare, clinical complication.
Material and Methods. We performed our research using the PubMed search engine provided by the National Centre for Biotechnology Information, having inserted 'iodinated contrast media', 'allergy', 'adverse reactions' as the keywords.
Results. Even though the modern iodinated contrast media are much safer than those used in the past, adverse reactions still occur in up to 1–3% of patients undergoing radiological procedures. Their range varies from skin changes, such as a macular rash, prurigo or urticarial, to the more severe multisystemic reactions including anaphylactic shock. The underlying mechanisms are still investigated and are not fully comprehended, although the most frequently accepted explanations include a systemic inflammatory reaction associated with increased histamine and tryptase levels, activation of memory T cells and both direct and indirect damage to the vascular epithelium. The significance of classic allergy tests has not yet been fully established. The associated known risk factors are of various character and researchers have come with different, occasionally contradicting results regarding patients' age and gender, however, other factors have been more clearly described, and include concomitant conditions and medications.
Conclusions. The aforementioned data emphasizes the importance of clinical aspects of allergy to the iodinated contrast media for every practicing physician, as more and more medical specialties benefit from the advantages of modern vascular imaging.

Introduction

The discovery of electromagnetic radiation with the length of 0.01–0.05 nm (Roentgen rays) in 1895 allowed their use in medical diagnostics. X-rays initially proved to be applicable primarily in diagnosing bone diseases, whereas the differences in their absorption by soft tissues were frequently too small to show particular lesions. Therefore, shading agents were introduced in order to properly visualise the pathology of organs in the imaging of the digestive system, circulatory system or urinary tract.

ICMs (iodinated contrast media) are highly concentrated solutions with a low molecular weight. The intravenous contrast media typically contain 270 to 370 mg of iodine/ml, and their doses range from 50 to 150 ml in adults. In fact, it is believed that chemical compounds containing elements with an atomic number of 50–60 are best suited for X-ray diagnostics. The substances which are mostly used nowadays are presented in **Table 1** [1].

Contrast media diffuse rapidly and approximately 70% of the administered dose disappears from plasma within 2–5 minutes after injection. These compounds are eliminated mainly via glomerular filtration (90% of the dose present in urine after 24 hours). Furthermore, the degree of protein binding is small (1–3%), non-specific and applies to water-soluble agents [2–5].

Currently, mostly iodine- and gadolinium based contrast agents are used in modern radiology. Iodine-based media can be divided according to their osmolarity (hiper-, izo- and hipo-), ionicity (ionic and non-ionic), as well as to the number of benzene rings (monomer and dimer). Nevertheless, the safest media are mostly non-ionic and either hypo- or isotonic, as they show significantly less adverse reactions in comparison to their hipertonic counterparts. Nowadays, more than 600 million radiological examinations are currently performed annually worldwide, out of which 40–70 million require the use of various contrast media.

Material and Methods

We performed our research using the PubMed search engine provided by the National Centre for Biotechnology Information, having inserted 'iodinated contrast media', 'allergy', 'adverse reactions' as the keywords.

Epidemiology of hypersensitivity to ICMs

Extensive research conducted in the 1980s allowed to assess the incidence of mild, immediate reactions in 3.8–12.7% of patients receiving high osmolality, ionic ICM injections, as well as in 0.7–3.1% of patients receiving low osmolality nonionic ICMs. As a result, the incidence of serious immediate adverse reactions was estimated at 0.1–0.4% for ionic ICMs and 0.02–0.04% for non-ionic ICMs. The mortality rate is 1 in 100,000 contrast-enhanced examinations, and in spite of the generally higher intensity of response to the ionic agents as compared to the non-ionic ones, it is not statistically significantly different for both ICM groups [2].

The incidence assessment of delayed adverse reactions is slightly more difficult, as indicated by a large discrepancy in the obtained percentages: 0.5–23%. If different, frequently uncharacteristic, adverse reactions occur hours or even days following the diagnostic procedure using ICM, the

Table 1. Osmolality, iodine ratio and iodine content in the iodinated contrast agents [1]

Name	Type	Osmolality [mOsm/kg H_2O]	Iodine ratio	Iodine content [mg/ml]
metrizoate 370 (Isopaque)	ionic monomer	2100	0.5	370
diatrizoate (Renografin)	ionic monomer	1570	0.5	300
iopromide 370 (Ultravist)	non-ionic monomer	774	3.0	370
iohexol 300 (Omnipaque)	non-ionic monomer	672	3.0	300
iomeprol 350 (Iomeron)	non-ionic monomer	618	3.0	350
iohexol 240 (Omnipaque)	non-ionic monomer	518	3.0	240
iodixanol 320 (Visipaque)	non-ionic dimer	290	6.0	320

Iodine ratio: ratio of iodine atoms to particles in solution; Serum osmolality: 285–295 mOsm/kg

actual assessment of a cause-and-effect relationship may pose some difficulty. According to the majority of researchers, such skin lesions in the form of various types of rash clearly suggest the relationship with exposure to ICMs, and their incidence is estimated at 1–3%.

The risk factors for hypersensitivity to ICMs are varied. In fact, *the occurrence of an adverse reaction after the exposure to contrast medium in the past* is considered to be the most vital predisposing factor. Moreover, it is estimated that administering the same or a similar ionic ICM to such a patient involves a risk of reacting again in 21–60% (according to some studies 16–44%) cases, whereas if a person receives a non-ionic agent, the risk of an adverse reaction decreases nearly tenfold. Other risk factors *for an immediate reaction* include:

- **history of allergy**: the most serious risk factor in this group is asthma [2][6–8];
- **female gender**: an ambiguous and discussed risk factor – according to some reports important for anaphylactoid reactions, according to other reports – for delayed reactions [2–3, 5–7, 9];
- **race:** British studies indicate a significantly higher risk of ICM hypersensitivity in Indians compared to the inhabitants of northern Europe or Africa [9];
- **age:** literature data are inconclusive – Japanese studies suggest higher incidence of hypersensitivity in young individuals (20–29 years), while according to the British studies, young adults are more likely to experience adverse reactions of mild or moderate severity, whereas older age groups are more likely to suffer severe reactions [6, 9];
- **route of administration of the contrast medium**: risk factors are quite rarely analysed, however, the intravenous route appears to involve a higher risk of adverse reactions in comparison to the intra-arterial administration [10];
- **comorbidities:** the major predisposing factors include cardiovascular diseases (coronary heart disease, rhythm disorders, cardiomyopathies, pulmonary hypertension, hypertension, previous myocardial infarction), as well as mastocytosis, accompanying viral infection on the day of exposure to ICM, and the autoimmune diseases (e.g. systemic lupus erythematosus) [2–9];
- **concomitant medications:** mainly beta-blockers (according to Lang D. et al. the increased severity of anaphylaxis was observed in patients receiving beta-blockers due to an increased propensity to bronchospasm and a decreased cardiac contractility with perpetuation of hypotension and bradycardia) [8]

Factors predisposing to the occurrence of a *delayed* reaction to ICMs mainly comprise: an adverse reaction to ICMs in the past, concomitant recombinant IL-2 treatment (for instance, due to metastatic renal cell carcinoma or melanoma), elevated serum creatinine level (>2 mg/dL) and a positive history of contact allergy [2–3, 5–7].

Proposed mechanism of hypersensitivity to ICMs

The main mediator involved in the etiopathogenesis of immediate adverse reactions appears to be histamine, which fills the granules of mast cells and basophilic granulocytes. The release of the mediator probably occurs through 2 main mechanisms: explosive degranulation associated with the presence of allergen-specific IgE antibodies, as well as through non-immunity reactions (strictly dependent on the agent dose, to which the cells are exposed). Furthermore, basophils appear to have a greater tendency to release mediators under the influence of non-specific factors than tissue mast cells, whereas in the course of reactions mediated by the elements of the immune system, the simultaneous release of histamine and tryptase occurs. In fact, basophils and mast cells show differences in the content of tryptase in granules (<0.05 pg/cell and 12–35 pg/cell, respectively). Determining plasma histamine concentration shortly after the ICM reaction allows to assess the degree of release of this mediator *in vivo*, while the measurement of serum tryptase concentration, if elevated, suggests the stimulation of mast cells [11].

Early adverse reactions appear mostly 5–15 minutes after the administration, whereas delayed ones – within 3 hours up to 2 days hereafter. [2]

According to the Norwegian researchers, T cells are actively involved in the pathomechanism of at least some of the delayed ICM reactions. The clinical picture of this type of reaction is characteristic and includes primarily cases of maculo-

papular skin changes. On the histopathological examination of the skin sample taken from the site where a positive skin test result was obtained with ICM present, there is usually a rich inflammatory infiltration present, consisting of lymphocytes and acid-absorbing granulocytes, as well as features of keratinocyte apoptosis. According to some researchers, the evidence of a significant role of T cells is the fact that adverse reactions to ICMs are more frequent in patients previously treated with IL-2 and in patients with systemic lupus erythematosus. Therefore, it appears that these factors may lower the lymphocyte activation threshold by increasing cytokine production and stimulation of monocytes. Moreover, the obtained positive results of diagnostic tests, such as SPT (skin prick test) and IDT (intradermal testing) with delayed reading, frequently constitute an important evidence of the contrast-specific T cells involvement in the adverse. It is also known that ICMs have the ability to stimulate the proliferation of *in vitro* lymphocytes (obtained from patients with a history of adverse reaction), and T-cell clones ($CD4^+$ and $CD8^+$) specific to a particular causative ICM are obtained from the cultures of these cells. In addition, in contrast to patients presenting symptoms of immediate hypersensitivity to ICMs, patients who have experienced a delayed reaction often present reactivity not only to causative ICM in the subsequent diagnosis, but also to many other contrast agents, which results from the apparent presence of T cells, characterised by a wide panel of cross-reactivity [12–16].

A rare type of a delayed reaction to ICMs is vasculitis. According to some researchers, the essence of this phenomenon may be the induced by ICM precipitation of the circulating immune complexes present in the skin vessels. So far, it has been impossible to obtain positive intradermal tests with ICM, or to confirm the presence of serum IgG and IgM antibodies showing affinity for ICM molecules in patients presenting with signs of vasculitis. Therefore, the abovementioned reaction mechanism requires further clarification [16].

"It has been proven that T lymphocytes are stimulated by increased IL-5 production, which is a growth stimulating factor for acid-absorbing granulocytes. Hence, in some patients eosinophilia can be observed in blood samples, regardless of the coexisting symptoms [17–18]".

Literature reports dealing with the etiopathogenesis of adverse reactions following contrast media are varied and often contradictory. The controversy is particularly related to the pathomechanism of immediate reactions. It is agreed that these reactions are predominantly associated with the massive release of histamine and other mediators from basophils and mast cells. Nevertheless, the degranulation of these inflammatory cells may be the result of various factors: direct membrane interaction of ICM (especially if the osmolality of the compound is significant), activation of the complement system, or it may be associated with an IgE-dependent reaction [4, 20–24].

Some studies indicate that the majority of adverse reactions to ICM, in particular those of minor severity, may be related to the direct, non-specific effects of ICM molecules. On the other hand, in more severe cases, which occur less frequently, the involvement of an immediate mechanism with IgE antibodies is suspected. However, many authors have long (1950s) denied the inducing effect of ICMs on the production of IgE class antigen-specific antibodies. There are many arguments against it, including the fact that ICMs are not bound by plasma and tissue proteins, and the likelihood of these compounds forming complete protein-hapten conjugates is very low. Moreover, the occurrence of hypersensitivity to ICM at its first application in some patients is also puzzling [6, 17, 25].

In contrast, only a few studies have been able to confirm the presence of serum IgE class antigen-specific antibodies with reference to ICM molecules. In patients with a history of early, severe ICM reaction, some authors observed the coexistence of the elevated circulating histamine and tryptase, positive skin tests, and detectable serum IgE antigen-specific antibodies with respect to the causative contrast medium. This, in turn, with some additional elements of medical history (greater severity of the reaction upon re-exposure and failure of the premedication used) is characteristic of IgE-weighted reaction. According to Gell and Coombs, the mechanism of I hypersensitivity reactions may also be supported in some cases by the correlation of the histamine release rate with the severity of the adverse reaction and a similar rate of recurrence of ICM reactions after previous exposure, as in patients

presenting with symptoms of IgE-dependent allergy to the venom of *Hymenoptera* insects, who were subjected to a provocation test with an allergen (39%). However, it should be emphasised that the percentage of patients who did not show a reaction to ICM at the first administration, but reacted with symptoms of hypersensitivity at the subsequent exposure, is estimated at about 21% [4, 6, 17, 21–23, 26, 27].

The relatively frequent phenomenon of hypersensitivity to ICMs following the first administration in individuals previously not exposed to contrast agents, still remains unexplained. It seems that, in this case, ICMs do not elicit an initial immune reaction, but instead interact with the easily activated memory T lymphocytes, which possess matched receptors. However, the time for an adverse reaction to occur will depend on the individual number of such cells in each patient. Furthermore, some researchers also suggest the possibility of earlier sensitization of the patient to compounds resembling the ICM molecule, for instance halogen derivatives of the benzene ring present in food additives (e.g. erythrosine – a cherry-red food dye), pesticides and herbicides; nevertheless, the initially published observations were not supported by further research [2, 3, 5].

There are a few literature reports relating to the described aspects. In fact, Stellato et al. [28] evaluated *in vitro* the degree of histamine, tryptase and prostaglandin D2 and C4 leukotriene released from human mast cells from the lungs, skin and heart muscle. The authors emphasise the heterogeneity of the reactivity of cells with various origins (for instance, pulmonary mast cells, but not skin mast cells, were degranulated when exposed to ioversol and ioxitalamic acid). Moreover, an important factor favouring the release of mediators from basophilic granulocytes was the hyperosmolarity of ICM, whereas for mast cells such a clear relationship was not found.

Peachell and Morcos [29] observed the in vitro release of histamine from basophils, pulmonary mast cells and cutaneous mast cells from healthy volunteers following various ICM, with a significant positive correlation with the osmolality of ICM, the dose of the agent, and the ICM exposure duration. Thus, it also appears that stronger degranulation of these cells occurs under the influence of ICM with a greater chemical complexity of the molecule.

In a recently published critical analysis of the effects of in vitro coronary angiography, Mansi [30] have emphasised that this is undoubtedly an invasive procedure, as a result of which there is a direct nonphysiological contact of the ICM solution with the vascular endothelium, In addition, foreign bodies in the form of polyurethane or polyethylene catheters also have a direct impact on the endothelium. Transient replacement of blood by ICM may result in a decrease of NO production in response to the mechanical stimuli and vasodilation, but also to an P-selectin expression increase within the endothelium, as well as to an increase in leukocyte adhesion, as well as an increase in the concentration of post-inflammatory cytokines (TNF-α). Intravenous administration of ICM has affects the concentration of various vasoactive substances: there is an increase in the release of kallikrein, bradykinin, serotonin, leukotriene B4 and, particularly importantly, histamine. In addition, an increase in the concentration of C-reactive protein, serum amyloid protein A (serum amyloid protein A – SAA) and IL-6 is observed in patients with unstable angina pectoris following coronary artery imaging without any complications. Therefore, it can be concluded that both mechanical and chemical stimuli acting in the course of coronary artery imaging with the use of ICM elicit a transient inflammatory reaction. According to the author, although millions of coronary angiography procedures are performed annually with a low rate of acute complications, it is also crucial to address the possible distant effects of intense release and interaction of non-inflammatory substances, depending on the initial degree of activation of the immune system. In fact, it is possible that subsequent coronary angiography procedures have a post-inflammatory effect, contributing to the progression of coronary artery atherosclerosis. However, little is known regarding the actual clinical implications of the described phenomenon in relation to the subsequent adverse hypersensitivity reactions to ICM.

It was found that mast cells constitute a crucial element of the ongoing inflammatory process within atherosclerotic plaques, in particular those located in coronary vessels. The mast cell density appears to be directly proportional to the severity of the atherosclerotic process. In fact, mast cell activation may be the result of complex interactions with the associated lymphocytes and mac-

rophages, and may also stem from stress. Furthermore, some authors consider tryptase to be a valuable screening marker for the risk of stable angina pectoris in asymptomatic patients. It may also serve as an exponent of the effectiveness of drugs aimed at stabilising atherosclerotic plaque in patients with the already diagnosed stable angina pectoris.

Clinical signs of hypersensitivity to ICMs

Depending on the responsible pathomechanism, the clinical manifestation of adverse reactions to ICMs is varied (**Table 2**). Immediate hypersensitivity reactions represent the most common (in nearly 70%) cause of urticaria and angioedema, whereas in more severe cases the symptoms affect the respiratory and cardiovascular systems, and also include the anaphylactic shock [2].

As mentioned above, delayed reactions are mostly manifested by maculopapular skin lesions (in more than 50% of cases), and the possible symptoms of erythema, delayed urticaria, sometimes accompanied by scaling. Typically, these reactions are self-limiting and not too severe, although there are also reports in the literature of severe SJS (Stevens-Johnson syndrome), TEN-type (toxic epidermal necrolysis) reactions, or vasculitis caused by ICM. Additionally, biphasic reactions (signs of a delayed reaction with the associated angioedema of the face) have also been reported rarely.

It is also vital to note that other types of adverse reactions to ICM may occur, which are not directly related to the hypersensitivity, such as induced hyperthyroidism. [1]

Diagnostic procedures for the suspected hypersensitivity to ICM

In 2005, researchers from the EAACI Interest Group, dealing with medication hypersensitivity (ENDA – European Network on Drug Allergy), developed a valuable set of recommendations for patients diagnosed with hypersensitivity to ICM [2]. It is known that the management will be slightly different in relation to the acute reaction, and other diagnostic elements will have to be taken into account in the case of a delayed reaction. A thorough interview allows for the preliminary assessment of the nature of the reaction based on the time since the intravenous ICM administration to the adverse reactions occurrence (immediate reaction: up to 1 hour, delayed reaction from 1 hour to 7 days). Additionally, the *Ring and Messmer* scale (1997) [24] is effective in the assessment of the clinical condition in the course of an acute reaction. On the other hand, the intensity of a delayed reaction can be assessed on the basis of the simple system proposed by ENDA (**Table 3**).

Further diagnostic procedures in adverse reactions to ICM include:

› during or shortly after the reaction
  – determination of **histamine** and **tryptase concentration levels** – particularly useful in immediate adverse reactions

Table 2. Clinical manifestation of hypersensitivity to ICMs, including immediate and delayed reactions

Immediate reactions	– Pruritus – Urticaria and angioedema – Sudden erythema (flush) – Vomiting, diarrhoea – Rhinitis/congested nose – Voice alteration, cough – Dyspnoea, tachycardia, arrhythmia, hypotension – Shock, cardiopulmonary arrest
Delayed reactions	– Pruritus – Urticaria and angioedema – Skin lesions: maculo-papular, spotty – Stevens-Johnson Syndrome – Lyell's syndrome – Graft versus host reaction – Vasculitis

Table 3. Clinical assessment of a delayed adverse reaction to ICM

Reaction severity	Characteristics
Mild	No treatment required
Moderate	There is a rapid improvement after the started treatment and there is no need for hospitalisation
Severe	The reaction requires the patient to be hospitalised, is life-threatening or is the cause of death

- peripheral blood laboratory analyses of renal and hepatic functions: it is crucial to bear in mind that other organs apart from the skin may become involved in the adverse reaction
- assessment of the peripheral eosinophilia using the Carpentier method [18, 19]
- assessment of lymphocyte activation exponents: CD25, CD69, HLA-DR (flow cytometry) and determination of CD25 serum levels (soluble IL-2 – IL-2sR receptor) involving the immunoenzymatic method, which are mainly used for scientific purposes

› after the period of remission
- skin prick tests with the undiluted contrast medium
- intradermal tests with diluted ICM: 1:10,000 to 1:10 – for the immediate-type reactions
- epidermal patch tests with the undiluted contrast medium – for the delayed-type reaction
- determination of IgE antigen-specific serum concentration: currently no commercial kits for routine measurements are available and the effectiveness of the test still requires assessment in further studies
- assessment of basophil activation: CAST ELISA method showed an increased release of cysteinyl leukotrienes both in *in vitro* and *in vivo* by ICM in patients who showed symptoms of an adverse reaction
- lymphocyte Transformation Test (LTT): requires appropriate laboratory conditions and experience (for a detailed description of the procedure, see the section on the diagnosis); it is not used in the routine clinical practice.
- provocative trials: in the 1970s, a pattern of intravenous, gradual provocation was proposed, consisting of 0.1 ml doses of subsequent ICM dilutions (starting from 1:10,000), administered at a 15-minute interval until a concentration of 1:1 was reached, then applied in the volume of 1 and 5 ml; the trial may be performed before a full dose of ICM is administered to the patient, and is definitely helpful in identifying patients at risk of adverse reactions; however, it is very

Table 4. The proposed treatment for various forms of allergy to ICM

Urticaria			
Mild reaction (scattered or transient pattern)			
No treatment			
May consider:	Diphenhydramine	25–50 mg p.o.	Or other approved antihistamines
	Fexofenadine	180 mg p.o.	
Moderate and severe reactions			
Monitoring vitals	Preserving i.v. access		
May consider:	Diphenhydramine	25–50 mg p.o. / i.v.	Or other approved antihistamines
	Fexofenadine	180 mg p.o.	
Diffuse erythema			
Monitoring vitals	Preserving i.v. access	Oximetry	Oxygen by mask (6–15 l/min)
Hypotension			
	I.v. fluids (0.9% NacL or Lactated Ringer's)	1,000 ml fast	
Consider:	Epinephrine (i.v)	0.1–1.0 mg	
	Epinephrine (i.m.)	0.3 mg	If iv. Access unavailable
Bronchospasm			
Monitoring vitals	Preserving i.v. access	Oximetry	Oxygen by mask (6–15 l/min)
	Beta-agonist inhaler (i.e. salbutamol)	4–10 puffs (100 mcg/dose)	Or 2.5–5.0 mg using nebulizer

time-consuming and therefore rarely useful in the routine clinical practice.

Treatment

The treatment of allergic reactions following the application of contrast media varies depending on the clinical situation. To summarise it more clearly, it has been presented in **Table 4** [10, 26, 31].

Conclusions

1. The currently used non-ionic, low-osmolar ICMs are characterised by high safety, and rarely cause adverse reactions.
2. Multicentre studies are required to assess the pathomechanism of adverse reactions to ICM, as well as to assess the value of diagnostic tests. An adequate number of patients needs to be analysed.
3. In patients presenting with symptoms of an adverse reaction of mild severity, skin tests performed during the remission period are often negative and do not account for an unambiguous inference of the IgE-dependent mechanism of the immediate reaction.
4. When using tryptase as a marker of anaphylactic reaction to ICM, the possibility of increased baseline levels of this mediator in patients with angina pectoris undergoing coronary angiography and PCI should be considered.

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