



Mini review

Contrast allergies for neurological imaging: When to proceed

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Abstract: Contrast-enhanced neuroimaging is often necessary for the diagnosis and care of patients with diseases of the central nervous system. Although contrast is generally well tolerated and allergy to contrast is rare, allergic reactions can be severe and life threatening. Therefore, physicians should take care to prevent severe contrast allergy. In this review, we will discuss contrast allergy as well as potential strategies to reduce the risk of severe reactions in patients who require neuroimaging techniques with contrast. First, we discuss the clinical presentation and pathogenesis of contrast allergy and the risk factors associated with reactions. We then review methods to reduce the risk of future contrast reactions through improved patient education and documentation strategies, use of alternate imaging modalities or contrast media, premedication, and desensitization.

Keywords: contrast; allergies; neurologic imaging; protocols; allergy preparation

1. Introduction

Neuroimaging employs imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) to assess the structure and function of the CNS, diagnose diseases, determine prognosis and proper treatments, and plan or guide surgical interventions [1–5]. CT detects how X-rays differentially traverse and attenuate through fluids and tissues to construct a

series of cross-sectional images in three planes, allowing for synthesis of a three-dimensional image [6,7]. Relatively short scan times make CT an invaluable tool in emergency situations. Non-contrast CT is used for evaluation of brain infarcts, hemorrhages, hydrocephalus, herniation, and skull or vertebral fracture [8]. Contrast can be utilized in traditional CT scans to allow for better tissue differentiation and identification of pathological structures such as masses or infections [8]. In addition, continuous X-ray imaging with contrast can be used in digital subtraction angiography (DSA) to evaluate the cerebral vasculature as well as to identify pathological blood flow [9–13]. DSA is used to diagnose and evaluate intracranial aneurysms, arteriovenous malformations, cerebral vasospasm, and other cerebrovascular abnormalities [12]. The most used contrast media in X-ray-based modalities such as CT and DSA are iodinated contrast media, which contain a benzene ring with three iodine molecules which block X-rays and allow for visualization.

MRI uses a powerful magnet to align protons in one plane and a radiofrequency to disrupt that alignment. The MRI machine then detects the time and energy required for hydrogen atoms to realign with the magnetic field in a process called relaxation. This information can in turn be used to infer local tissue properties. MRI offers superior tissue resolution compared to CT and does not use ionizing radiation [5,14]. However, MRI is more expensive and takes longer to complete [14]. MRI has broad clinical applications in neuroimaging and can be used to visualize structural, inflammatory, myelin, and proliferative pathology in the CNS [5,15,16]. Contrast-enhanced MRI allows for visualization of small lesions, cerebral vasculature, primary and secondary CNS tumors, and blood-brain barrier integrity [5,17–19]. The most used contrast media for MRI are gadolinium-based contrast media which have unpaired electrons that allow for a high magnetic moment and shortened T1 relaxation time [5].

Although contrast media is an important, and often necessary tool for neuroimaging, contrast can rarely cause allergic reactions, which can be severe or even life threatening. Understanding these reactions and how to reduce their incidence or severity is crucial. In this paper, we will discuss the physiology behind contrast allergy and ways to reduce the risk of allergic reactions such as documentation of previous allergic reactions, use of alternate imaging strategies, premedication, and desensitization.

2. Contrast hypersensitivity

Iodinated contrast for X-ray-based imaging and gadolinium contrast for MRI imaging can cause acute or delayed hypersensitivity reactions. Whether immediate reactions to iodinated and gadolinium contrast agents are allergic or allergic-like is still controversial [20]. Most immediate reactions appear to be allergic-like or anaphylactoid, and although they closely resemble type I hypersensitivity reactions, they lack hallmark characteristics such as mediation through anti-contrast IgE and requisite prior exposure [21–25]. The pathogenesis of allergic-like reactions to contrast agents is still being elucidated and is most likely multifactorial. It is hypothesized that contrast media can bind to nonspecific sites on IgE molecules of mast cells and basophils, resulting in their activation [22,24–27]. Additionally, local changes in osmolarity and ion concentrations and complement activation by contrast media can also activate mast cells and basophils [26,28,29]. Mast cell and basophil activation results in the release of histamine, tryptase, and inflammatory mediators [21–23,27,30]. Although most patients with immediate reactions to contrast have an

allergic-like reaction, some patients do appear to have a more classic type I hypersensitivity reaction mediated by anti-contrast IgE [31–36].

The clinical manifestations of immediate allergic and allergic-like reactions are similar. Immediate reactions begin within the first hour after contrast administration and can range from mild to severe. A mild reaction, which is usually self-limiting and does not require intervention, can present with symptoms such as limited urticaria or pruritis [21,37,38]. A moderate reaction can cause symptoms such as throat tightness, facial edema, and bronchospasm. Severe reactions can be life threatening and can present with pulmonary edema, anaphylaxis, and hypotension [21,38]. In terms of treatment, there is no distinction between allergic and allergic-like reactions. For mild reactions, treatment is not usually necessary and can consist of symptom management. Severe reactions should be managed by ensuring a patent airway and adequate oxygenation and administering epinephrine and corticosteroids [21,22,28,37,39].

Non-immediate reactions to contrast media occur between 1 hour and 1 week post contrast administration and are T cell-mediated type IV hypersensitivity reactions [22,23,28,38,40,41]. Delayed reactions are traditionally milder than acute reactions and can present as urticaria, maculopapular rash, pruritis, nausea, vomiting, diarrhea, and rarely hypotension [22,28,38]. However, potentially life-threatening cases of severe cutaneous drug reactions such as acute generalized exanthematous pustulosis, Stevens–Johnson Syndrome, and toxic epidermal necrolysis have been reported [22,28,38,40,42–45].

The greatest risk factor for allergic and allergic-like reactions to a contrast agent is a personal history of a reaction to that agent [21,40,46]. Because allergic-like reactions are not mediated by antibodies to the contrast, one reaction does not guarantee a repeat reaction, but does increase the risk [39,47,48]. Atopy and asthma may also increase one's risk of allergic-like immediate reactions [39,47,48]. It may be reasonable to use a contrast with a lower risk of reaction, such as low-osmotic or nonionic contrast media in patients with atopy and asthma due to their increased risk [22,49–51]. However, current guidelines recommend against contrast media restriction based on asthma and atopy [37]. Despite common thinking and inclusion in screening criteria, a seafood allergy does not increase the risk of allergy to contrast media [48,52–54]. While seafood, like many other food products, contains iodine, it is unlikely that IgE or T cell-mediated reactions to contrast media are due to antibodies against iodine [54,55]. Other characteristics have been described as increasing one's risk for developing contrast allergy, including female gender, other drug allergy, mastocytosis, severe cardiovascular disease, high serum creatine, and the use of certain medications like beta blockers, ACE inhibitors, and IL-2 [28,37,46,47,56–61]. However, studies have shown that these do not increase one's risk enough to contraindicate receiving contrast or otherwise alter the standard of care [37,47,48].

3. Contrast hypersensitivity prevention

3.1. Documentation of prior allergic-like or allergic reactions

Collecting an accurate history of previous allergic reactions to a contrast medium is essential in assessing a patient's risk for a reaction to that contrast or similar contrast media. However, obtaining that information can be difficult. Ruff C et al. found that in a cohort of 307 patients who reported a history of contrast allergy, 98.4% of participants were unable to name which contrast agent or what

type of contrast caused their reaction [62]. Moreover, only about 40% of participants knew the name of the facility where they had the reaction or what city they were in at the time, making it difficult for a provider to request the appropriate health records to determine which contrast to avoid [62]. Educating patients about their reactions so that they can inform medical professionals about their histories during future scans could help prevent repeat reactions. In addition, documentation of allergic or allergic-like reactions to contrast in the electronic medical record needs improvement [63,64]. Studies looking at the quality of contrast reaction documentation have found most records are in free text, which can be difficult to find, especially if the medical professional is not specifically looking for it [63,64]. It is important to include clear and correct information about which contrast caused the reaction as well as the characteristics of the reaction [63]. Along with patient education and proper documentation, implementing “time out” checklists prior to scans involving contrast may be an effective way to reduce medical error and repeat reactions to contrast [65].

Skin tests and drug provocation tests may be helpful for patients with a history of reaction to contrast when imaging without contrast is not an option [20,28,38,40,44,48]. For patients with a history of immediate reactions who have records or knowledge of which contrast agent caused their reaction, a skin prick test can be used to determine which other contrast agents may be safe to use as alternatives [20,28,40,44,48]. For patients who do not know which contrast agent they reacted to, an intradermal test should be performed as a panel to determine which contrast likely caused the reaction, followed by a skin prick test to determine which other agents are likely safe to use [20,28,40,44,48]. Patients with a history of mild delayed reactions to contrast should have either a patch test or an intradermal test that is read after 24–48 hours to confirm allergy to the specific contrast agent, followed by a skin prick test to determine potentially safe alternatives [20,28,40,44,48]. While skin tests offer promise as a potential screening and diagnostic tool in high-risk patients, there is still limited and mixed evidence to support their efficacy. The variable sensitivities between studies could be problematic as patients could still suffer a severe reaction to a contrast agent despite a negative skin prick test [20,28,31,40,44,48,66–73]. However, skin tests should be completed to ensure that allergic reactions are not missed [31,48]. The drug provocation test may be helpful in confirming the results of the skin test [20,28,40,44,48]. The drug provocation test can potentially elicit a severe reaction so it should only be performed for patients who have already had a negative skin prick test to that agent [20,28,40,44,48]. Furthermore, it is possible that the drug provocation test could elicit temporary desensitization, causing a false negative [48]. Patients with a history of reaction to contrast should be given alternate contrast agents with caution, and treatment should be on hand in the event of a severe reaction despite a negative skin test and negative drug provocation test [20,28,40,44,48]. Guidelines regarding skin tests and drug provocation tests still vary greatly, and further research should be conducted to establish a consensus on the role of skin and drug provocation testing in the care of patients with previous contrast reactions.

3.2. Use of alternate contrast or imaging strategies

Contrast should be avoided in patients with a history of immediate or delayed reactions to a specific contrast agent, especially when that reaction was severe [22,37,66,74]. If a patient requires imaging, the physician and patient should discuss risks and benefits to receiving or forgoing contrast in their specific case. If possible, scans should be conducted without the use of contrast or via other imaging modalities [22,74]. The cross reactivity of contrast agents is still being elucidated and may

differ among patients [23,28,36,38,55,75]. Some studies support switching to a contrast agent with a different structure [37,40,76–81]. Skin testing and drug provocation tests may also help guide physicians as to which contrast agent may be safe to use. However, there are patients who still have repeat reactions despite these measures [73].

3.3. Premedication

For patients with a history of reaction to contrast, premedication is another strategy to reduce the risk of reaction in situations when contrast is required. The use of premedication is controversial [20,22,28,40,44,48,52,77,78,81–84]. Studies have shown that premedication is useful in reducing the incidence of, but not preventing, immediate and non-immediate reactions to contrast [22,52,80,85–87]. Furthermore, patients can still have life threatening reactions despite premedication, and contrast should be used with caution in patients with a history of reaction [22,52,73]. Premedication may be more effective when combined with other prevention strategies [73,76,79,88]. In cases where imaging needs to be planned for high risk individuals, the American College of Radiology recommends one of two strategies:

Repeated doses of 50 mg oral prednisone at 13 hours, 7 hours, and 1 hour prior to contrast administration with 50mg of diphenhydramine administered 1 hour prior to contrast [37,41,87].

Or

Repeat doses of 32 mg oral methylprednisolone at 12 and 2 hours prior to contrast administration with or without the addition of 50 mg diphenhydramine 1 hour prior to contrast [37,89].

In some cases, high risk patients may need urgent imaging that impedes the ability to perform a 12–13 hour premedication regimen. Accelerated strategies can be used in these situations, however, there is limited evidence to support their efficacy [37]. The American College of Radiology suggests these accelerated premedication regimens:

Intravenous methylprednisolone sodium succinate 40 mg or hydrocortisone sodium succinate 200 mg administered every 4 hours for an average duration of 4–5 hours, plus intravenous diphenhydramine 40mg 1 hour prior to contrast administration [37].

Or

Intravenous dexamethasone sodium succinate 7.5 mg every 4 hours for an average duration of 4–5 hours, plus intravenous diphenhydramine 50 mg 1 hour prior to contrast administration [37].

Or

Intravenous methylprednisolone sodium succinate 40 mg or hydrocortisone sodium succinate 200 mg, plus intravenous diphenhydramine 50 mg administered 1 hour prior to contrast administration. This combination may be used in emergent situations where a 4-hour pre-medication window is not feasible. However, there is not yet evidence to support the efficacy of this strategy [37].

3.4. Desensitization

For patients with significant histories of allergic-like reactions to radiocontrast media who may be at risk for breakthrough reactions even with premedication, and for whom no other therapeutic alternative is available, rapid intravenous desensitization may offer an effective preventative strategy. Several case reports have shown that administering serial dilutions of iodixanol, an iodine-containing

nonionic radiocontrast agent, in escalating doses (until the total amount of exposed drug reaches the dose required by the intervention) every 10 minutes beginning two hours before coronary angiography successfully prevented subsequent immediate contrast reactions in high-risk patients [78,90,91]. Adverse effects of the desensitization process, if present, were minor (pruritus) and managed with diphenhydramine [90,91]. The mechanism of desensitization is still debated, but one hypothesis is that exposure to increasing amounts of antigen alters the actin framework in mast cells such that inward calcium flux is prevented and mast cells cannot degranulate [92,93]. The duration of this strategy's effect is linked to the half-life of the desensitizing radiocontrast medium; for iodixanol, this suggests it needs to be repeated for interventions more than 48 hours apart [91].

4. Conclusions

Contrast media greatly enhances the diagnostic utility of neuroimaging techniques such as CT and MRI, but rarely can elicit hypersensitivity reactions in certain patients which can be life threatening. Contrast reactions are diverse both in mechanisms and severity, and treatment should be informed foremost by the patient's presenting symptoms. The most predictive risk factor for future reactions is a history of reactions, so the importance of obtaining and documenting an accurate history of reactions in the medical record cannot be overstated. For individuals with elevated risk, recommendations for alternative contrast or and/or imaging modalities, sensitivity testing, premedication, and rapid desensitization may be appropriate based on the unique needs of the patient and following a thorough risk-benefit discussion between the patient and provider.

Disclaimer

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

Anna Fusco, Logan Pucci, and Kevin Pierre made final revisions. Adam Wolberg wrote the first draft for the section reviewing iodinated contrast for CT. Coulter Small wrote the first draft of the introduction section. John Cerillo wrote the first draft of the allergy preparation and pre-medication section. Mohammad Reza Hosseini wrote the first draft of the section discussing gadolinium contrast for MRI. Brandon Lucke-Wold formulated the initial paper outline and made final revisions.

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