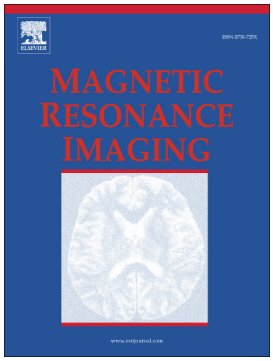

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Ingrid B. Boehm

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Classification of gadolinium-based contrast agents (GBCAs)-adverse reactions

Ingrid B. Boehm

Department of Diagnostic, Interventional and Pediatric Radiology, Inselspital, University of Bern, Switzerland

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Correspondence: Dr. Ingrid B. Boehm
Assistant Professor
Department of Diagnostic, Interventional and Pediatric Radiology
Inselspital
University of Bern
Freiburgstrasse
3010 Bern, Switzerland
Phone: +41-31-632 24 35
Fax: +41-31-632 48 74
E-mail: ingrid.boehm@insel.ch

Letter-to-the-Editor

Now we use gadolinium-based contrast agents (GBCAs) for more than three decades in clinical radiological routine. Consequently, we have comprehensive experiences with these compounds and data of a huge number of papers. Therefore, we know that GBCAs are safe in most instances, but can also induce different kinds of adverse reactions such as hypersensitivity reactions, gadolinium depositions including nephrogenic systemic fibrosis (NSF) as well as contrast-induced acute kidney injury [1-5]. Unfortunately, a classification of these side effects has not yet been published. Consequently, knowledge concerning the categorization of GBCA-dependent reactions is sparse. Therefore, the goal of this paper is to present a classification, and thereby, to elucidate the background of adverse reactions following GBCA-injection.

First, adverse drug reactions in general and GBCA-reactions in particular should be subdivided into type A and B reactions [6-8] (Figure).

Type A reactions are dose-dependent, predictable, and dependent on the chemical properties of the drug [6]. GBCAs can induce three different type A reactions (Figure): 1) mild toxic reactions, formerly called physiological reactions [9], 2) contrast-induced acute kidney injury (CI-AKI) [5], and 3) deposition-dependent reactions.

Mild toxic reactions can manifest as skin redness (erythema), nausea/vomiting and/or head ache for example [9].

Although less known, GBCAs like iodinated contrast media can also induce CI-AKI [5].

Finally yet importantly, GBCAs attracted attention by causing depositions in different organs / organ systems and in different severity grades. The mildest form is the so-called gadolinium storage condition (GSC) [2]. Patients with this kind of Gd-deposition lack both clinical symptoms and failure of organ functions [10]. The next severe condition is the so-called gadolinium deposition disease (GDD) [3]. The term created by Semelka and colleagues means that the patients suffer from clinical symptoms such as arthralgia, muscle weakness, burning sensation, paraesthesia, heat-/cold feeling, fever, flu-like symptoms, fatigue, nausea/vomiting, headache, dizziness, brain fog, and/or visual impairment [3]. Objective symptoms are rare, and comprise only of cutaneous nodules covered by skin redness located on distal extremities, also known as gadolinium-associated plaques (GAP) [11].

Type B reactions are hypersensitivity reactions and thereby these reactions are not predictable, dose-independent and independent of the GBCAs chemical properties [6]. Hypersensitivity reactions may be either allergic or non-allergic [12]. In most cases, GBCAs are responsible for immediate reactions, but non-immediate (delayed) reactions are also possible [13]. While allergic reactions produce a positive skin test result, non-allergic reactions do not. One should also realize that GBCA-allergy persists for several months, and can disappear afterwards [14]. Life-long GBCA-allergy is unusual.

Why do we need such a classification?

Although most physicians and scientists do not like papers dealing with the background of nomenclature or classification systems, such information is very important for both clinical routine and scientific projects. In clinical routine settings, knowledge of the GBCA-classification helps to understand clinical reactions, ensures the exact documentation of them, and thereby enable us to conduct a safe

management when the patient needs a re-exposure [15]. The planning and conducting of clinical studies is only possible if clear in- and exclusions do exist. This is easily possible when we use the suggested classification (Figure).

Conclusion

Taken together, GBCA-induced adverse reaction can be subdivided into two main groups, namely type A and type B reactions. The first category comprises of three further subgroups of reactions (mild toxic reactions, depositions with or without clinical symptoms, and contrast-induced acute kidney injury). The second category contains hypersensitivity reactions with either allergic or non-allergic background. Moreover, hypersensitivity reactions may occur as immediate or non-immediate (delayed) reactions.

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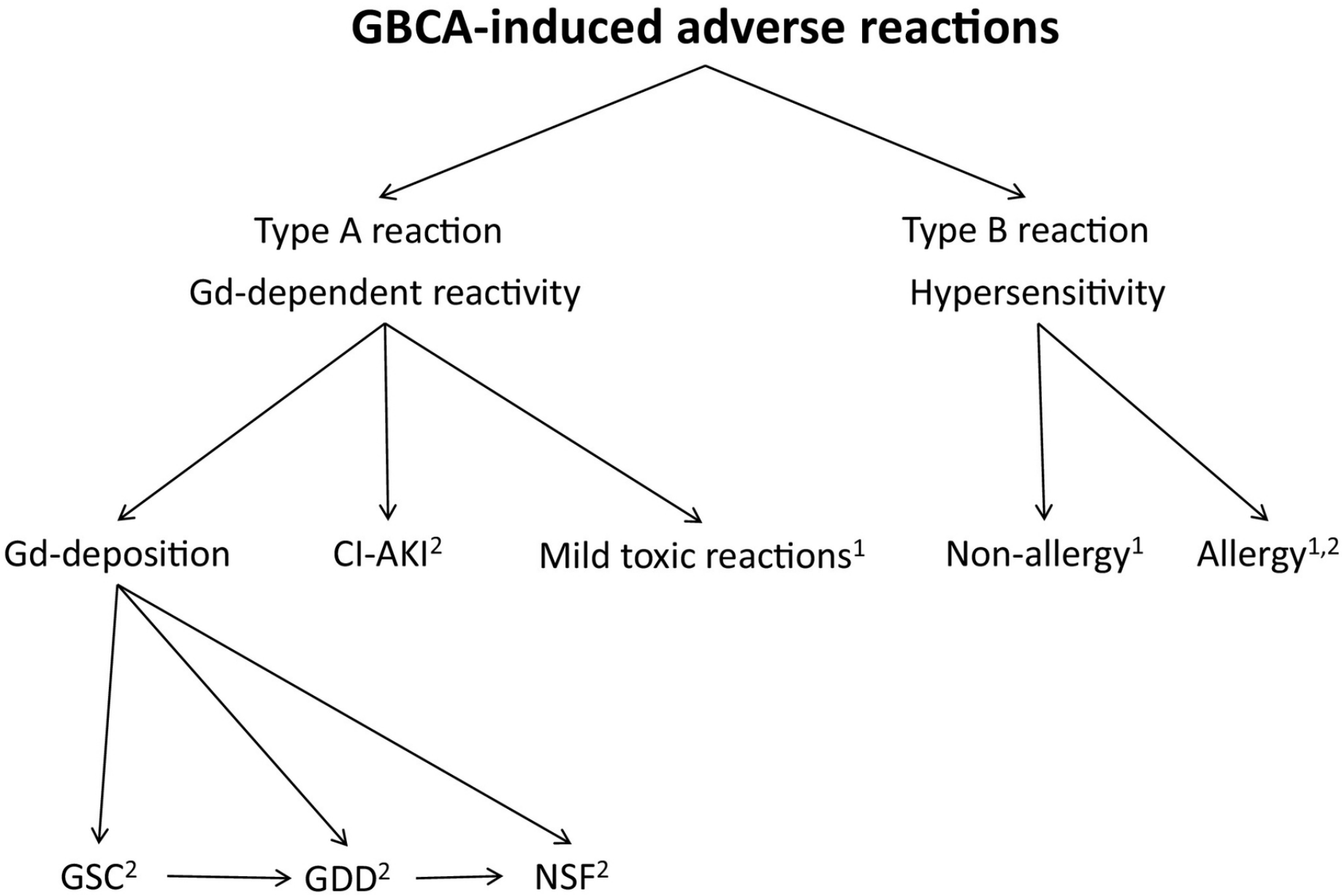
GBCA-induced adverse reactions
Type A reaction
Type B reaction
Gd-dependent reactivity
Hypersensitivity
Gd-deposition
CI-AKI[2]
Mild toxic reactions[1]
Non-allergy[1]
Allergy[1,2]
GSC[2]
GDD[2]
NSF[2]

Figure 1