Gadolinium retention — 5 years later...

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Received: 5 September 2019 / Revised: 5 September 2019 / Accepted: 16 September 2019 / Published online: 16 January 2020
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It has been 5 years since the parenchymal retention of gadolinium used for contrast-enhanced MRI was first suggested to occur in the central nervous system (CNS). In 2014, Kanda et al. [1] and Errante et al. [2] both showed increasing unenhanced T1-weighted signal intensity in certain portions of the brain (e.g., dentate nucleus and globus pallidus) after multiple administrations of Group I gadolinium-based contrast agents (GBCAs) [3]. Subsequent studies have confirmed the presence of elemental gadolinium from GBCAs retained in the CNS and have demonstrated a higher propensity for retention for linear than for macrocyclic contrast agents. Recent investigations using analytical chemistry methods (e.g., inductively coupled plasma — mass spectroscopy [ICP-MS]) to assess tissues from people exposed to a variety of gadolinium chelates have confirmed that all currently used GBCAs (Group I, Group II and Group III) demonstrate some degree of long-term retention, including in people with normal kidney function [4–6]. Although it has been known for decades that gadolinium is retained in other tissues (e.g., bone and liver) [7, 8], the discovery that it was being retained in the CNS raised serious safety questions related to the permeability of the blood–brain barrier and potential effects on brain function that are in the process of being investigated.

Gadolinium retention is not unique to adults. Hu et al. [9] demonstrated increased signal intensity in the globus pallidus and dentate nucleus in 21 children receiving between 5 and 37 group GBCA administrations. Similar imaging findings have been reported by other authors [10–13]. A small case-control study by McDonald et al. [14] used transmission electron microscopy to confirm intracranial gadolinium retention in tissue samples from pediatric autopsy specimens following Group I GBCA administration. Similarly, the current study by Stanescu et al. [15] in this issue of *Pediatric Radiology* used ICP-MS to document elemental gadolinium in brain tissue following linear and macrocyclic GBCA administration, including ionic and nonionic macrocyclic GBCA, and after single and multiple doses.

Other than nephrogenic systemic fibrosis (NSF), which occurs exclusively in people with severe kidney impairment and nearly always from Group I GBCA administration, no agreed-upon specific symptom or constellation of symptoms can be attributed to gadolinium retention in the brain or elsewhere in the body. This is despite more than 450 million intravascular administrations of GBCAs to date [6]. While approximately 200 adults have reported to the United States Food and Drug Administration nonspecific symptoms (e.g., headache, fatigue, pain, mental slowing [“brain fog”]) following GBCA exposure, including within 24 h after a single dose, no causal link has been established, and there is no scientifically accepted non-NSF retention-related disease [6]. However, lack of evidence is not conclusive evidence of absence. For example, the relationship between nephrogenic systemic fibrosis and GBCA administration was not recognized until 2006, more than 20 years after GBCAs were in widespread clinical use [16, 17].

So, what is a pediatric radiologist to do? While no specific disease is recognized, and the specific molecular composition of retained gadolinium is unknown, free gadolinium in the body is potentially neurotoxic and generally undesirable [18]. Therefore, in this period of uncertainty, perhaps the most practical approach is to treat GBCAs like ionizing radiation. By this we mean to follow an ALARA (as low as reasonably

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achievable) approach [19]. Like gadolinium retention, the specific harms of medical ionizing radiation are not fully known. But perhaps both should be minimized as much as is reasonable while remembering that the diagnostic benefits generally exceed the risks for indicated examinations. GBCAs should not be administered freely regardless of medical appropriateness, but instead should be used when clinically indicated, like any other medication. Recognition of gadolinium retention should prompt more vigorous assessment of the necessity of GBCAs for common indications, consideration of gadolinium retention alongside other characteristics in choice of GBCA, and development of non-inferior non-contrast techniques that decrease the necessity of GBCAs in imaging protocols.

Overreaction also should be avoided. For several decades, iodinated contrast media were considered a common important cause of acute kidney injury and, as a result, likely tens of thousands of people were deprived of their possible benefits. Today, we understand that the independent risk of acute kidney injury related to these agents was greatly overstated [20, 21], meaning that many people were subjected to the harms of suboptimal or delayed diagnostic imaging without personal benefit. We do not want to make this same mistake with GBCAs and deprive our patients of their potential benefits if their use is indeed appropriate.

Compliance with Ethical Standards

Conflicts of interest None

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