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EDITORIAL

Gadolinium deposition in the brain: another concern regarding gadolinium-based contrast agents

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Life is continuously confronting us with new issues and sometimes breaking our routine. One case in point is the curious way radiologists' knowledge about the benefits and risks of gadolinium-based contrast agents (GBCAs) continues to evolve. Significantly improving detection and characterization of lesions in a broad spectrum of diseases, GBCAs have become integral aides to magnetic resonance imaging (MRI) for almost three decades. Because free gadolinium is toxic, it needs to be chelated with a ligand ion to facilitate its excretion through the kidneys. Currently available GBCAs have different chemical properties primarily determined by the chelating ligand molecule. These agents had initially been believed to be risk-free with rapid elimination from the body, and administered to millions of patients somewhat indiscreetly for over a decade after the clinical approval of gadopentate dimeglumine in 1988. This naive belief was disproved by a string of studies revealing a relationship between the use of GBCAs and the development of nephrogenic systemic fibrosis (NSF) in 2006 (2, 3). The accrued data convincingly showed a causal link between GBCAs and the risk of NSF in patients with severely compromised renal function (glomerular filtration rate <30 mL/min). Due to insufficient excretion of GBCA in patients with poor renal function, the administered contrast material (gadolinium chelate) stays long enough in the body to pose the risk of dissociation (dechelation) which consequently triggers the cascade of events resulting in NSF. An editorial published in the December 2006 issue of this journal addressed the issue of NSF and provided some timely recommendations (4). Further studies revealed that the chemical structure of GBCAs matters in the development of NSF, and the risk is much higher with nonionic linear chelates, such as gadodiamide and gadoversetamide, due to rapid release of gadolinium (dechelation) in these agents. Conversely, macrocyclic GBCAs are more resistant to dechelation and considered to be more stable. These studies modified the practice of intravenous MRI contrast agent use and paved the way for the creation of new standards in the use of GBCAs. Many international and national authorities established guidelines for the use of GBCAs in MRI. These guidelines primarily categorized agents into three categories as low risk (macrocyclic agents), intermediate risk (ionic-linear chelates) and high risk (nonionic-linear chelates) for the development of NSF. Adherence to these guidelines and adoption of new contrast-enhanced MRI protocols, which restrict the administration of high-risk GBCAs only to subjects with normal renal function and replace these agents with more stable GBCAs in high-risk patients, resulted in a dramatic decline in the incidence of NSF (5). Nevertheless, it should be emphasized that there are considerable differences between GBCAs with similar structure. For instance, no unconfounded NSF case has been reported following administration of ionic-linear gadobenate dimeglumine whereas two NSF cases were reported after unconfounded administration of nonionic-macrocyclic gadobutrol (6).

In 2014, radiologists (as well as clinicians) were in for another stunning report, this time of a study performed in Japan (7) implying deposition of gadolinium in the brain manifested as dose-related T1 shortening in the globus pallidus and the dentate nuclei in patients who had been administered repeated previous doses of gadodiamide and/or gadopentetate dimeglumine. This novel observation was subsequently confirmed by Errante et al. (8) who reported dose-dependent T1 shortening in the dentate nucleus in subjects with normal kidney and liver function who had serial prior administration of gadodiamide. Two recent studies performed on autopsy specimens proved that T1 shortening results from gadolinium retention in neuronal tissues of the global pallidus, thalamus, dentate nucleus, and pons (9, 10). It was shown that gadolinium deposition was detectable with as few as four lifetime

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doses of gadodiamide in all patients regardless of renal or hepatobiliary dysfunction (10). The retained gadolinium was shown to accumulate mainly in the endothelial walls while a smaller amount of it did cross the blood-brain barrier and deposited within neuronal interstitium.

Similar to the link between NSF and GBCAs, the growing body of data indicates that the molecular structure of GBCAs also matters in T1 shortening in the neuronal tissue. Two recent studies reported in 2015 from Japan (11) and Germany (12) demonstrated that high signal intensity in dentate nucleus was associated with the repeated previous administrations of the ionic-linear agent (gadopentetate dimeglumine in both studies), but not with the repeated prior administrations of the nonionic-macrocyclic (gadoteridol) and ionic-macrocyclic (gadoterate meglumine) agents. These findings imply that the observed T1 hyperintensity may represent a consequence of the dissociation of gadolinium from its ligand molecule.

What is the responsibility of radiologists at this stage? What has been learned from the GBCA-NSF linkage mostly holds true for gadolinium retention in intracranial neuronal tissues. The chemical structure of the GBCAs is directly related to retention; the amount is lowest in macrocyclic GBCAs, high in ionic-linear GBCAs, and highest in nonionic-linear GBCAs (6). More worrisome is that gadolinium deposition occurs in all subjects exposed to GBCA regardless of renal or hepatobiliary dysfunction. Although the clinical significance of gadolinium accumulation remains unclear, the reported findings are troublesome and radiologists need to take this issue into account and employ caution when administering GBCAs. As gadolinium deposition in brain may occur even in subjects with normal renal and hepatobiliary function, in contrast to NSF, we need to avoid overusing contrast-enhanced MRI, and justify that each gadolinium-enhanced MRI is truly indicated. Then, we should sparingly choose more stable GBCAs in each subject to reduce the risk of potential long-term detrimental effects. Since neuronal gadolinium deposition is significantly dose-dependent, we should make every effort to administer the lowest reasonable amount of GBCA. Children and young adults deserve extra attention in using GBCAs, and appropriate measures should be taken to minimize the cumulative gadolinium deposition over a patient's lifetime. Surprises are unavoidable in the vagaries of life, mechanisms of which are poorly understood despite all the advances in science. Always bearing in mind the dictum "primum non nocere", we need to employ caution and carefully weigh the risks and benefits of our decision to use GBCAs.

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