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CLINICAL

Nephrogenic systemic fibrosis: MRI hazards in patients with severe renal impairment

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TITLE Cardiac and vascular metal deposition with high mortality in nephrogenic systemic fibrosis

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SUMMARY

Nephrogenic systemic fibrosis (NSF) is a systemic illness comprised of fibrosis and systemic inflammation, and is reported almost exclusively in patients with severe renal impairment who are exposed to gadolinium-based contrast agents. It was first reported in the literature in 2000,[1] but the link to gadolinium-containing contrast agents was only established in 2006.[2] Characteristic features include extensive cutaneous fibrosis similar to that seen in scleroderma but sparing the face and neck and without scleroderma-associated autoantibodies.

As a relatively new entity it is now well known to renal physicians, but perhaps not to those in other specialties managing patients with coincidental severe acute or chronic renal impairment. Magnetic resonance imaging (MRI) scans using gadolinium need to be requested with caution for such patients.

This paper describes retrospective clinical and laboratory data on 32 patients with NSF exposed to gadolinium-based contrast agents. The authors describe a high mortality and a variable but often early onset of NSF after gadolinium exposure. The particular focus of this paper is the finding of widespread systemic deposition of gadolinium and other metals, perhaps most importantly in the heart and large blood vessels.

The median follow-up after NSF diagnosis was 226 days, during which period ten patients (31.3%) died. The median time between gadolinium exposure and NSF diagnosis was 83.5 (4–555) days, and the median time between diagnosis and death was 112 (37–263) days. The conditions cited as 'associated with death' were as follows: cardiovascular disease (n=9); sepsis (n=5); discontinuation of dialysis (n=1). As expected, cardiovascular disease included congestive heart failure, hypotension, cardiac arrhythmias, sudden death and myocardial ischaemia. Interestingly, one patient developed limb ischaemia and another posterior ischaemic optic atrophy causing blindness.

The authors report detailed information in three patients who went on to have a complete post-mortem examination. The first developed NSF four days after gadolinium exposure and died one month later. The second patient was diagnosed two months after gadolinium exposure and died after nine months, and the third died of congestive heart failure and recurrent arrhythmias. All three patients were receiving dialysis. Metal deposition was measured using inductively coupled plasma-mass spectroscopy (ICP-MS) and confirmed by X-ray fluorescence of tissue samples. The authors describe significant quantities of gadolinium in many tissues apart from the skin – for example, the heart, aorta, kidney, liver and lungs. Interestingly, they also describe increased iron and aluminium deposition in heart muscle and aorta. It is worth noting, however, that control data was from the skin and blood vessels of patients having either skin biopsy for basal cell carcinoma or artery biopsy for suspected temporal arteritis. These control cases did not have renal failure and had not received gadolinium-based contrast agents. We are not told if the patients had received oral or intravenous iron supplements (a common occurrence in dialysis patients).

Having confirmed widespread metal deposition, the authors go on to postulate that cardiac and vascular deposition of gadolinium and, perhaps, iron plays an important part in the cause of death in patients with NSF. We know that gadolinium can induce the mobilisation of iron, which can in turn lead to transmetalation of gadolinium chelates and liberation of free gadolinium, which is, of course, toxic. The deposition of free gadolinium and iron may induce an inflammatory response in blood vessels, the heart and skin, and the subsequent tissue injury may potentiate NSF.

OPINION

This paper gives us a good insight into the diagnosis and prognosis of a rare but important disease at a time when the use of MRI is increasing rapidly. It postulates a link between iron and gadolinium deposition in vascular tissue, which I feel invites further study.

However, the practising clinician is left with the question of how to balance the risk and benefit of gadolinium-based contrast when requesting an MRI scan on a patient with acute renal failure, one receiving dialysis or perhaps even with severe but stable chronic renal failure. When considering this question we should remember that cases of NSF are reported 'in the low hundreds' and that more than 26 million gadolinium-enhanced MRI scans were performed in the US alone in 2006. The risk of NSF is concentrated around patients on dialysis or those who are very unwell and perhaps acidotic (which may also increase the risk) with acute renal failure. The precise risk of developing NSF after gadolinium-enhanced contrast MRI is not known for dialysis patients or for the much greater population of patients with a low glomerular filtration rate (<30 ml/min).

Clearly, in these cases the diagnostic value of the scan has to be carefully weighed against the risk of NSF, and discussion with a radiologist regarding the need for a gadolinium-based contrast agent or, indeed, the alternative (but not risk-free) use of iodine-based contrast in CT is highly recommended.[3] It may also be possible to reduce the risk of NSF by the choice of gadolinium chelate. The majority of cases of NSF have been linked to two agents, gadodiamide and gadopentate.

Our current approach is to use gadolinium chelates thus far not described with unconfounded cases of NSF – namely Dotarem, Vasovist or Multihance – in patients with an estimated glomerular filtration rate of less than 30 ml/min. Patients on haemodialysis can have dialysis arranged within a few hours of the study (typically three dialyses clear almost all the gadolinium), although it has to be said that no benefit is proven for dialysis in the treatment or prevention of NSF. Patients receiving peritoneal dialysis are only scanned with extreme caution and after discussing alternative approaches (as peritoneal dialysis does not remove gadolinium).

Finally, as NSF registries develop, it is likely we will learn more about the obviously complex interplay between factors associated with severe renal failure, gadolinium and other metal deposition and the consequent inflammatory process that follows.

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