NEPHROGENIC SYSTEMIC FIBROSIS: A HIGHLY RELEVANT AND SIGNIFICANT ADVERSE EFFECT ASSOCIATED WITH GADOLINIUM BASED MRI CONTRAST AGENTS

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ABSTRACT

Nephrogenic systemic fibrosis (NSF), also known as nephrogenic fibrosing dermopathy (NFD), is a disease of fibrosis of the skin and internal organs reminiscent but distinct from scleroderma or scleromyxedema. It is caused by gadolinium exposure used in imaging in patients who have renal insufficiency. Nephrogenic systemic fibrosis always occurs in patients with renal insufficiency who have had imaging studies (e.g., magnetic resonance angiography) with gadolinium, a contrast agent used in imaging studies. Nephrogenic systemic fibrosis resembles scleroderma and eosinophilic fasciitis clinically and scleromyxedema histopathologically. Patients with nephrogenic systemic fibrosis may develop large areas of indurated skin with fibrotic nodules and plaques. Flexion contractures with an accompanying limitation of range of motion also can occur.

KEYWORDS: Nephrogenic Systemic Fibrosis, Gadolinium, MRI, Contrast Agent.

INTRODUCTION

The occurrence of nephrogenic systemic fibrosis is related to the exposure of patients with renal insufficiency to gadolinium in association with imaging studies. The chelated forms of the less stable gadolinium chelates might have a significant role, but it appears that dissociated gadolinium's gradual release is pivotal in the development of nephrogenic systemic fibrosis and its sometimes delayed onset.[1]

The pathophysiology of nephrogenic systemic fibrosis is related to the exposure of patients with renal insufficiency to gadolinium in association with imaging studies. Evidence for a link between nephrogenic systemic fibrosis and gadolinium was first described in a case series of 13 patients, all of whom developed nephrogenic systemic fibrosis after being exposed to gadolinium.[2] The mechanism by which this occurs is not known, but it seems to involve a cell termed a circulating fibrocyte that is stimulated by gadolinium.[3] Endothelin-1/endothelin receptor signaling plays a role in the calcification and fibrosis of nephrogenic systemic fibrosis.[4]

Toll-like receptors (TLR), in particular TLR4 and TLR7, play a role in the development of nephrogenic systemic fibrosis.[5] Thomsen et al.[6] noted that more than 90% of proven nephrogenic systemic fibrosis cases are related to gadodiamide (Omniscan) and some to gadopentetate (Magnevist).[7] As such, gadoversetamide (OptiMARK) and gadopentetate dimeglumine (Magnevist) should not be used for imaging in patients with renal impairment. MultiHance and ProHance, similar brands, should also likely not be used.

The safety of gadopentetate linear product might be no different from macrocyclic preparations such as gadodiamide (Omniscan), but guidelines should be followed in all gadolinium products.[8] The macrocyclic contrast agents gadobutrol (Gadovist/Gadavist) and gadobenate dimeglumine (MultiHance) should be used only following guidelines. It is possible that Gadovist, Dotarem, and Prohance are safer, but this does not justify changing guidelines.[9] While evidence data showing a benefit for prompt hemodialysis after gadolinium imaging are lacking, this is a justified precaution.

Similar guidelines from the FDA and the American College of Radiology (ACR) state that gadolinium use with an approximate glomerular filtration rate of 30-44 mL/min per 1.73 m² should be used with extreme caution. Gadolinium can be deposited in almost any tissue in the body after its use for imaging studies. Gibson et al.[10] noted 2 reports with apparent multiorgan fibrosis with involvement of skeletal muscle, myocardium, the lungs, the kidneys, and the testes. Of interest, a condition that resembles nephrogenic systemic fibrosis is eosinophilia-myalgia syndrome, which is also caused by an exogenous substance. Edward et al.[11] found that fibroblasts derived from skin affected by nephrogenic systemic fibrosis synthesize elevated levels...
DISCUSSION

The condition known as nephrogenic systemic fibrosis is a progressive chronic condition affecting individuals with renal impairment. It is characterized by the development of extensive skin and connective tissue thickening, leading to decreased mobility and even organ dysfunction. The precise mechanism triggering this condition remains unclear, but it is believed to involve a complex interplay of factors, including the exposure to gadolinium-based contrast agents used in medical imaging. Patients with a history of gadolinium exposure are at increased risk of developing this condition, particularly those with pre-existing conditions such as diabetes or renal failure. The inflammatory response triggered by gadolinium exposure appears to be linked to the development of skin fibrosis and systemic sclerosis-like changes.

The increased risk of Nephrogenic Systemic Fibrosis was supported by a cohort study involving patients with chronic kidney disease, which reported a significantly higher incidence of this condition in those who had been exposed to gadolinium contrast agents. This finding underscores the importance of continued monitoring and appropriate risk assessment for patients undergoing imaging procedures.

Patients with a history of gadolinium exposure should be closely monitored, and alternative imaging modalities may be considered if possible. Further research is needed to better understand the underlying mechanisms and develop strategies for preventing or treating this debilitating condition.


