

**NEPHROGENIC SYSTEMIC FIBROSIS: A HIGHLY RELEVANT AND SIGNIFICANT  
ADVERSE EFFECT ASSOCIATED WITH GADOLINIUM BASED MRI CONTRAST  
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Article Received on 08/07/2017

Article Revised on 28/07/2017

Article Accepted on 18/08/2017

**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 (eg, 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.<sup>[1]</sup>

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.<sup>[2]</sup> 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.<sup>[3]</sup> Endothelin-1/endothelin receptor signaling plays a role in the calcification and fibrosis of nephrogenic systemic fibrosis.<sup>[4]</sup>

Toll-like receptors (TLR), in particular TLR4 and TLR7, play a role in the development of nephrogenic systemic fibrosis.<sup>[5]</sup> Thomsen et al<sup>[6]</sup> noted that more than 90% of proven nephrogenic systemic fibrosis cases are related to gadodiamide (Omniscan) and some to gadopentetate (Magnevist).<sup>[7]</sup> 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.<sup>[8]</sup> 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.<sup>[9]</sup> 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 m<sup>2</sup> 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<sup>[10]</sup> 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<sup>[11]</sup> found that fibroblasts derived from skin affected by nephrogenic systemic fibrosis synthesize elevated levels

of sulphated glycosaminoglycans, in particular hyaluronan, compared with normal control samples, while serum from the one patient with dermatomyositis and from the 2 patients with nephrogenic systemic fibrosis stimulated sulphated glycosaminoglycans synthesis, including hyaluronan synthesis, by both control and patient fibroblasts. Metformin use might influence nephrogenic systemic fibrosis, but this is not proven.<sup>[12]</sup>

The amount of gadolinium needed to induce aberrant production of hyaluronic acid seems to be minimal. According to an abstract presented by Dr. Susie Mukherjee reported at the 2007 annual meeting of the British Association of Dermatologists, only tiny concentrations of gadolinium are needed to stimulate hyaluronan synthesis by fibroblasts. Both 10-mmol/L and 1-mmol/L concentrations of gadolinium caused a 2.3-fold increase in hyaluronan synthesis.<sup>[13]</sup> Parsons et al performed immunohistochemical studies using antibodies to transglutaminase-2, factor XIIIa, transglutaminase isopeptide, and the histiocyte marker CD68 on 5 archived skin biopsy specimens of nephrogenic systemic fibrosis.

Parsons et al<sup>[14]</sup> found that dermal fibroblasts and histiocytes of nephrogenic systemic fibrosis expressed transglutaminase-2, CD68, factor XIIIa, and transglutaminase isopeptide. They posited that this represented increased expression, activation, or concomitant activation and expression of transglutaminases in nephrogenic systemic fibrosis.

## DISCUSSION

Patients need to understand that nephrogenic systemic fibrosis is not a life-threatening disease and that it lacks effective treatment. Patients should also be warned about the increased risk of falls and subsequent fractures.

Spontaneous resolution is described in some reports, typically coincident with improved/resolved renal disease. In most patients, nephrogenic systemic fibrosis is a progressive condition. Many patients report stabilization and marginal improvement after years with the condition. Whether nephrogenic systemic fibrosis is a localized or systemic disease is not yet clear.

Nephrogenic systemic fibrosis appears linked to increased morbidity and mortality. Todd et al<sup>[15]</sup> found that 24-month mortality rates following examination were 48% and 20% in patients with and those without cutaneous changes of nephrogenic systemic fibrosis, respectively (adjusted hazard ratio, 2.9; 95% confidence interval, 1.4-5.9).

Within weeks of disease onset, many patients become dependent on a wheelchair because of contractures. Several patients have died because of complications from fractures after falls triggered by their mobility problems. Additionally, many patients report maddening pruritus

and/or causalgia. Finally, some patients experience flexion contractures if the disorder occurs over a joint.

## CONCLUSION

Gadolinium-based contrast agents were for many years considered safe, but this is no longer the case now. The least stable agents may trigger the development of nephrogenic systemic fibrosis (NSF), a generalized fibrotic disorder, in renal failure patients. The use of gadodiamide and gadopentetate dimeglumine is now contraindicated in Europe and Japan in patients who have a glomerular filtration rate less than 30 mL/min/1.73 m<sup>2</sup>, including those on dialysis.

The fear of NSF, however, should not lead to an enhanced MR imaging examination being denied when there is a good clinical indication to give a gadolinium-based contrast agent.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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