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Gadolinium-based contrast agents, erythropoietin and nephrogenic systemic fibrosis in patients with end-stage renal failure

Sir,

Nephrogenic systemic fibrosis (NSF) is a rare and debilitating disorder, which affects patients with kidney failure. An association with gadolinium-based contrast agents for magnetic resonance imaging (MRI) was found [1]. However, not all NSF patients had a prior gadolinium exposure [2]. Recently, an association of NSF and the use of erythropoietin was proposed [3]. Our aim was, thus, to investigate the use of gadolinium-based contrast agents and erythropoietin in haemodialysis patients with and without NSF.

Four patients in our dialysis unit developed NSF (between 2002 and 2006). We retrospectively compared those to all other patients requiring chronic haemodialysis ($n = 61$; data collection in August 2007). Besides demographic characteristics, we investigated haemoglobin levels, iron and erythropoietin supplementation, parameters of inflammation, Kt/V and exposure to gadolinium.

Table 1 gives the basic characteristics of patients and controls. There were no differences with regard to age, sex, number of previous kidney transplantations, cumulative time on haemodialysis or primary renal disease. The same was true for Kt/V. The haemoglobin levels were comparable, but NSF patients received higher doses of erythropoietin (331.1 $\pm$ 215.1 versus 133.3 $\pm$ 99.5 U/week/kg body weight; $P < 0.05$). In the NSF group, 4/4 of the patients received erythropoietin and in the control group 53/61 ($P > 0.05$).

In the NSF group, on average, more contrast enhanced MRIs had been performed [3.0 $\pm$ 1.2 per patient (range 2–4) versus 1.8 $\pm$ 2.0 per patient (range 0–10); the mean dose contrast agent 12.6 $\pm$ 5.4 versus 11.6 $\pm$ 4.6 mmol/MRI]. In the control group, the following contrast agents were used: gadopentetate dimeglumine 94 times, gadodiamide 9 times, gadobutrol 4 times and gadobenate dimeglumine once. In the NSF group, gadopentetate dimeglumine and gadodiamide were used six times each. The cumulative dose of contrast agent was higher in the NSF group (0.57 ± 0.14 versus 0.29 ± 0.37 mmol/kg body weight; $P < 0.05$). In the NSF group, the time from the last administration of a contrast agent to the first symptoms was 2 weeks till 5 months. Comparing those patients with a minimum of two MRIs (as this is the minimum number in the NSF group) patients in the NSF group, again, received higher doses of erythropoietin (331.1 $\pm$ 215.1 versus 128.1 $\pm$ 215.1 U/week/kg body weight; $P < 0.05$).

There is growing evidence for a pathogenic role of gadolinium ions as causing agents in the development of NSF [1]. However, not all patients with NSF have been exposed to gadolinum-containing contrast agents [2,5,6]. There seems to be a reasonable likelihood of additional (co-)triggers, which may-–alone or in combinations-–play a role in the pathogenesis of NSF. In some studies, an association between erythropoietin and NSF [3,7,8] could be found, while not in others [6,9]. One of the cardinal features of NSF is the presence of CD34+ fibrocytes [10]. These cells resemble bone marrow-derived progenitors. One hypothesis says that erythropoietin could drive the development of NSF by increasing the number of circulating haematopoietic stem cells and endothelial progenitor cells, thereby increasing the pool of CD34+ cells. These cells finally may enter the tissue and enhance the fibrotic process. Alternatively, the higher dosage might also reflect erythropoietin resistance in the presence of chronic inflammation, making higher dosages necessary to achieve equal levels of haemoglobin [3,4,11].

The findings of our study have to be interpreted cautiously. The number of NSF patients is small and whether the association with erythropoietin is causative or reflects erythropoietin resistance cannot be answered. However, even if gadolinium seems to be the major culprit in the development of NSF, there is no final proof and a number of questions remain open. The search for (co-)triggers in the development of NSF is strongly warranted. This is especially true in light of limited treatment options of this disabling disease.

Conflict of interest statement. None declared.

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Table 1. Basic characteristics and laboratory parameters

	Controls ($n = 61$)	NSF patients ($n = 4$)	P-value
Age (years)	58.2 ± 15.6	50.6 ± 18.5	0.36
Sex (m/f)	49/12	3/1	>0.05
Patients with prior KTX (*n*; range)	17 (1–4)	1 (3)	>0.05
Time of ESRD	4.5 ± 6.2	2.6 ± 3.3	0.56
Kt/V	1.1 ± 0.2	1.0 ± 0.3	0.36
Systolic blood pressure (mmHg)	138.6 ± 24.7	153.8 ± 21.7	0.23
Diastolic blood pressure (mmHg)	73.6 ± 15.0	81.3 ± 8.5	0.32
Antihypertensive drugs (*n*)	2.0 ± 1.7	1.3 ± 1.3	0.41
Primary renal disease			>0.05
Diabetic nephropathy	20 (32.8%)	2 (50%)	
Vascular nephropathy	7 (11.5%)	1 (25%)	
Glomerulonephritis	19 (31.1%)	–	
Intertitial nephritis	2 (3.3%)	–	
Reflux nephropathy	3 (4.9%)	–	
Tumour	3 (4.9%)	1 (25%)	
Others	2 (3.3%)	–	
Unknown	5 (8.2%)	–	
Haemoglobin (mg/dl)	12.0 ± 1.3	11.0 ± 1.0	0.15
Serum iron (μg/dl)	66.3 ± 28.9	35.5 ± 12.5	0.04
Transferrin (mg/dl)	184.7 ± 38.3	146.8 ± 20.0	0.06
Transferrin saturation (%)	26.4 ± 13.3	17.5 ± 6.9	0.19
Ferritin (ng/ml)	459.6 ± 349.4	536.0 ± 254.2	0.67
CRP	2.0 ± 3.0	2.7 ± 1.9	0.68

CRP: C-reactive protein; ESRD: end-stage renal disease; KTX: kidney transplantation.

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Cystatin C as a surrogate for glomerular filtration rate in the presence of proteinuria

Sir,

All methods for assessing glomerular filtration rate (GFR) have shortcomings. Serum creatinine has a reciprocal relationship to GFR that is related to age, race, sex and muscle mass and is affected by tubular secretion. Creatinine clearance requires a timed urine collection, and radio isotope and inulin clearance methods are expensive. Estimated GFR may only be valid in the steady state of chronic kidney disease (CKD) [1].

There has been much [2] interest in cystatin C, a serine protease inhibitor produced by all nucleated cells, freely filtered at the glomerulus and, although reabsorbed, apparently fully metabolized in tubular cells [3]. Serum cystatin C may be more sensitive to changes in GFR than serum creatinine [4,5].

Renal disease is often accompanied by proteinuria, the severity of which correlates with progression [6], possibly because protein in the tubular fluid injures tubular cells via mechanisms involving reactive oxygen species [7]. We hypothesized that proximal tubular injury by proteinuria might affect cellular handling of cystatin C, leading to an altered relationship to GFR.

We measured serum cystatin C in 65 nephrology-clinic patients, with and without proteinuria, using a latex-enhanced immunonephelometric assay based on rabbit polyclonal antibodies (Dade Behring, UK) with a ProSpec analyser (Dade Behring, UK). Urinary creatinine and protein were measured using standard chemistries on Roche Modular systems (Roche/Hitachi, Roche Diagnostics, Gmbh, Germany). GFR was estimated using the modification of diet in renal disease (MDRD) formula [8]. Patients were being treated for stable CKD secondary to primary glomerulonephritis (28%), diabetes (15%), vasculitis or lupus (8%), chronic pyelonephritis (6%), hypertensive nephrosclerosis (3%), miscellaneous conditions (16%) or unknown cause (24%). They were classified as proteinuric