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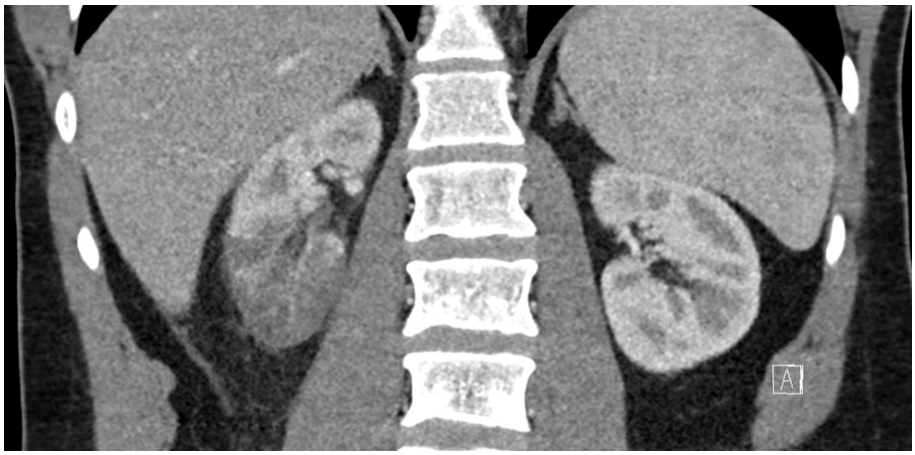

A young man with back pain; what is your diagnosis?

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Editorial office
Erasmus MC, University Medical Center Rotterdam
Department of Internal Medicine
's-Gravendijkwal 230
3015 CE Rotterdam
The Netherlands
Tel.: +31 (0)10-703 59 54
Fax: +31 (0)10-703 32 68
E-mail: p.l.a.vandaele@erasmusmc.nl
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VAN ZUIDEN communications

Van Zuiden Communications B.V.
PO Box 2122
2400 CC Alphen aan den Rijn
The Netherlands
Tel.: +31 (0)172-47 61 91
Email: mouton@vanzuidencommunications.nl
Internet: www.njm-online.nl

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EDITORIAL

To find glomerulonephritis you have to look for it

C.A. Stegeman

Department of Internal Medicine, Division of Nephrology, University Medical Center Groningen, Groningen, the Netherlands, email: c.a.stegeman@umcg.nl

Anti-neutrophil cytoplasmic antibodies (ANCA) associated small vessel vasculitis is a systemic auto-immune disease with widespread and highly variable clinical manifestations. Renal involvement, usually in the form of necrotising crescentic glomerulonephritis (pure necrotising renal vasculitis without glomerulonephritis is very rare), is frequently one of the manifestations of the disease and is encountered in the majority of patients at diagnosis.[1] The severity of renal involvement has both therapeutic and prognostic consequences. Most management guidelines determine the intensity of immunosuppressive therapy on the severity of vital organ dysfunction, which in many patients is defined by the level of renal failure.[1,2] In addition, the level of renal failure at diagnosis and especially the failure to regain renal function during induction therapy is associated with a worse outcome and high mortality.[3,4] So assessment of the presence and severity of renal involvement in ANCA-associated vasculitis is mandatory and an essential part of patient care and the selection of appropriate treatment.

The diagnosis of ANCA-associated vasculitis has been made more straightforward by the discovery of the high sensitivity and specificity of autoantibodies directed against proteinase-3 and myeloperoxidase.[5,6] Reliable assays to detect these antibodies are available. Also awareness of these diseases has probably increased over the last decades. It is conceivable that the diagnosis of ANCA-associated vasculitis is made more timely and that the proportion of patients with severe organ dysfunction including severe renal failure is declining and patients are diagnosed in an earlier and more limited phase of the disease. This view is illustrated by the finding of Houben et al. described in this issue of the journal that in 109 patients diagnosed with ANCA-associated vasculitis the median serum creatinine at diagnosis was low despite renal involvement in 61% of the patients at diagnosis.[7]

Most patients with ANCA-associated vasculitis will not present with visual or other overt signs of renal involvement: macroscopic haematuria is usually absent as one of the presenting symptoms and proteinuria is frequently mild, not leading to the clinical signs of nephrotic syndrome. This is also nicely illustrated by the paper by Houben as only 21 of the patients from their cohort were diagnosed by the renal department. This means that patients present with combinations of other signs and symptoms and are referred to other disciplines. Renal involvement, therefore, has to be actively investigated once the diagnosis of ANCA-associated vasculitis is suspected. This means that in every patient in whom the diagnosis of ANCA-associated vasculitis is seriously considered, assessment of renal function (serum creatinine, estimated glomerular filtration rate (eGFR), 24-hour urine creatinine clearance) and urinalysis (erythrocyturia and if present urinary microscopy for glomerular erythrocyturia and/or erythrocyte casts, proteinuria) should be performed.[1,2] As Houben et al. describe, it is worrying that renal involvement is not actively investigated in a proportion of patients with suspected or confirmed ANCA-associated vasculitis, not even in the weeks and months following the diagnosis. The 19 of 109 patients (22% in patients not diagnosed in the renal department) with ANCA-associated vasculitis not screened for renal involvement in their study had a lower serum creatinine (median 70 μmol/l, IQR 56-89 μmol/l) at diagnosis, which may have led to the misconception that a serum creatinine in the 'normal' range effectively excludes the presence of renal involvement. In addition, we have to repeat the message that a so called 'normal' serum creatinine is not the equivalent of normal renal function. Especially in an older population (mean age at diagnosis 62 ± 14 years in the cohort described by Houben) and in persons with a systemic inflammatory illness lasting for some time and leading to muscle wasting, serum creatinine levels can be deceptively low despite significant renal impairment.

As renal involvement is usually seen as a sign of more severe disease in ANCA-associated vasculitis, the failure to

recognise renal involvement early may lead to insufficient treatment of patients, which is suggested by the fact that cyclophosphamide induction therapy was given to only 37% of those not screened for renal involvement. Also the fact that, despite a lower serum creatinine at diagnosis, at three years of follow-up renal function as estimated by eGFR was clearly lower in patients who did not receive cyclophosphamide induction compared with those who did may point in that direction. Finally, it should be highlighted that even in the minority of patients with documented absence of renal involvement at diagnosis, during follow-up renal involvement may develop. In a recent series from our centre this was the case in 21%, while at least half of all relapses in patients with renal involvement at diagnosis show renewed renal activity.[4] This means that screening for renal involvement is not only mandatory in the diagnostic phase, but also is an essential part of assessment for disease activity during follow-up. This is essential to all of us who diagnose and treat patients with these diseases. To paraphrase one of the rules from 'The House of God' by Samuel Shem: you won't find renal small vessel vasculitis if you don't do a urinary sediment.

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REVIEW

Acute reactions to polysulfone/polyethersulfone dialysers: literature review and management

W.H. Boer[1]*, Y. Liem[2], E. de Beus[1], A.C. Abrahams[1]

[1]Department of Nephrology, University Medical Center, Utrecht, the Netherlands, [2]Department of Medicine, Section for Nephrology, Helse Møre og Romsdal – Ålesund Sykehus, Ålesund, Norway, *corresponding author: tel.: +31 (0)88-7557329, fax: +31 (0)30-2543493, email: w.h.boer@casema.nl

ABSTRACT

Acute dialyser reactions in patients treated by haemodialysis are uncommon. We present two cases of such reactions, both in patients using a polysulfone, steam-sterilised dialyser. Patient 1 suffered from recurrent attacks of acute dyspnoea, hypoxia and hypotension that occurred early in dialysis sessions, whereas patient 2 presented with unexplained episodes of severe hypotension and vomiting in the initial phases of dialysis. After switching to a cellulose triacetate dialyser, both patients became asymptomatic during all subsequent dialysis sessions, but intentional (patient 1) and accidental (patient 2) rechallenge with the polysulfone dialyser induced an immediate recurrence of the symptoms. A literature search yielded 30 additional cases that have been reported since the turn of the century. All dialysers that provoked acute reactions contained membranes belonging to the polyarylsulfone family (polysulfone/polyethersulfone, PSu/PESu). Manifestations, usually occurring within the first 30 minutes of dialysis, included dyspnoea (69%), hypotension (66%), hypoxia (44%), bronchospasm (25%), chest pain (22%), pruritus and/or urticaria (22%) and abdominal symptoms (22%). Of the 32 patients, 14 were switched to a different PSu/PESu containing dialyser, which resulted in cross-reactivity in 12 of them (~85%). They could be treated safely with dialysers containing substituted cellulose (n = 8) or polyacrylonitrile (n = 4). Sixteen patients were successfully switched directly to a dialyser containing substituted cellulose (n = 11), polymethylmethacrylate (n = 4) or polyacrylonitrile (n = 1). Two patients were lost to follow-up. As rechallenges may be harmful, patients with acute reactions to PSu/PESu membranes should not be further tested in a trial-and-error fashion with similar membranes, but be switched directly to a non-PSu/PESu dialyser.

KEYWORDS

Acute dialyser reaction, anaphylaxis, haemodialysis, polysulfone membrane, polyethersulfone membrane

INTRODUCTION

In the last decades of the previous century, acute dialysis reactions were common in patients treated by haemodialysis. They were related to the use of bio-incompatible, complement-activating dialyser membranes (often combined with hypoxia-inducing acetate-containing dialysate), ethylene-oxide (EtO) sterilisation of dialysers that caused IgE-mediated hypersensitivity or exposure to polyacrylonitrile (PAN) membranes that stimulated the production of bradykinin.[1] However, even in the current era, in which biocompatible dialysers are being used, bicarbonate has replaced acetate as a dialysate buffer and EtO sterilisation has been abandoned, occasional cases of acute dialyser reactions continue to be reported, also recently.[2,3]

We describe recent acute dialyser reactions in two patients treated by a polysulfone, steam sterilised dialyser. These cases prompted us to review the literature on acute dialyser reactions in the last decade to define their clinical characteristics, develop a management strategy and increase awareness of this potentially serious adverse event.

Patient 1

A 74-year-old male (diabetic nephropathy) was treated with haemodialysis with an F8-HPS polysulfone dialyser (Fresenius®). He was on an ACE inhibitor and aspirin. In February 2012, after seven months of stable treatment, he complained of dyspnoea immediately after starting dialysis. A week later he reported similar symptoms and abdominal pain four minutes after starting dialysis. His blood pressure dropped from 177/89 mmHg to

112/52 mmHg and the oxygen saturation was 91%. An ECG showed no arrhythmias or ischaemia. The ACE inhibitor was stopped. Thirty minutes into the next dialysis, dyspnoea and abdominal pain developed abruptly. The blood pressure was 180/100 mmHg and arterial pO_2 was 50 mmHg. Blood chemistry did not show haemolysis or infection and a chest X-ray was normal. During one of the episodes, the eosinophil count was elevated (1.29 x 10^9/l, normal < 0.40 x 10^9/l), but values of 0.68 and 0.87 x 10^9/l were measured during two other episodes, when platelet counts (245 and 290 x 10^9/l, respectively) were also within the normal range. We considered an allergic reaction to dalteparin (Fragmin®, Pfizer), the only drug given prior to the dialysis sessions. Despite switching to danaparoid (Orgaran®, Merck Sharp & Dohme), the dyspnoea occurred 30 minutes into the next dialysis. The blood pressure dropped abruptly from 132/60 mmHg to 98/54 mmHg and the pO_2 fell from a predialysis value of 88 mmHg to 55 mmHg (changes in O_2 saturation and pCO_2 from 97% to 87% and from 37 mmHg to 40 mmHg, respectively). Suspecting an allergic reaction to the F8-HPS dialyser, we switched to a dialyser with a different membrane, the Sureflux 150-L (Nipro®, cellulose triacetate) for the next dialysis. During this session, the patient remained asymptomatic and blood pressure, pO_2 and O_2 saturation remained stable within the normal range. The patient agreed to a rechallenge with the F8-HPS dialyser, which resulted in direct recurrence of dyspnoea. We interrupted the session immediately and restarted dialysis using the Sureflux 150-L dialyser, after which the symptoms abated. Dialysis sessions with the cellulose triacetate (CTA) dialyser were uneventful with a follow-up extending to December 2015.

Patient 2

A 69-year-old male (diabetic nephropathy) started haemodialysis in November 2015 using an F8-HPS polysulfone dialyser (Fresenius®). He was not on an ACE inhibitor, β-blocker or aspirin. The first two sessions were uneventful, the patient tolerating 1.8 litres of ultrafiltration and a 12% reduction in relative blood volume. During the 3rd dialysis, he started vomiting and briefly lost consciousness after 40 minutes. The blood pressure, which was 150/60 mmHg at the start of dialysis, was 129/65 mmHg shortly after the incident. Ultrafiltration had been 0.3 litres up to the incident, but there was no reduction in relative blood volume (change + 0.4%). An ECG showed no arrhythmias, the plasma troponin was normal. Dialysis was stopped. The next dialysis, performed without ultrafiltration, was uneventful. During the 5th dialysis, the patient became unwell after 50 minutes. His blood pressure, which was 155/76 mmHg at the start of dialysis, had fallen to 66/26 mmHg, despite zero ultrafiltration. During the 6th dialysis, the patient became unwell after 45 minutes and the blood pressure fell to 86/39 mmHg, although the ultrafiltration rate had been set to zero from the start of dialysis. After two uneventful sessions, he became hypotensive (blood pressure 70/40 mmHg) with severe nausea and vomiting after 30 minutes during the 9th dialysis. Up to this point, no volume had been removed by ultrafiltration. The tentative diagnosis of acute dialyser reaction was made and the patient was switched to a Sureflux 150-L dialyser (Nipro®, cellulose triacetate). The remainder of the dialysis sessions went without incident. After 20 uneventful dialysis sessions using the Sureflux dialyser, the patient was accidentally treated with an F8-HPS dialyser, and he became unwell and hypotensive (blood pressure 94/46 mmHg) 50 minutes into dialysis. The total follow-up after switching to the CTA dialyser is three months, in which the patient has remained asymptomatic. Unfortunately, no eosinophil or platelet counts were obtained during any of the acute dialyser reactions.

SUMMARY OF RECENT CASE REPORTS ON ACUTE DIALYSER REACTIONS

We found 30 cases of acute dialyser reactions in the literature since the beginning of the current century,[2-19] bringing the total to 32 cases (*table 1*). The mean patient age was 68.7 years (range 34-90 years), and 56.3% were males. In 17/32 cases (53.1%), reactions occurred in the first week after starting exposure to the offending dialyser, most often after the first contact. In the remaining 15 cases, however, the interval between first exposure to the dialyser and occurrence of symptoms was considerably longer (mean 11 months, range 1 to 36 months). In 24/32 cases (75.0%), the reactions occurred within the first 30 minutes of dialysis. In the remaining cases, symptoms occurred between 45 and 120 minutes after starting dialysis or became manifest very gradually. Reported manifestations were dyspnoea (69%), hypotension (66%), hypoxia (44%), bronchospasm (25%), chest pain (22%), pruritus and/or urticaria (22%) and abdominal symptoms (22%). Severe laryngeal oedema or stridor occurred twice. Cardiorespiratory arrest occurred six times (19%), and two patients (6%) died.

Table 1 shows that all dialysers that induced acute reactions contained membranes of the polyarylsulfonate family,[20] which includes polysulfone (PSu, 28 cases, 87.5%) and poly(aryl)ethersulfone (PESu, 4 cases, 12.5%). Fourteen patients were subjected to a different PSu/PESu containing dialyser at some point with a total of 18 trials (*figure 1*). In 16/18 (88.9%) of these trials (in 12/14 patients, 85.7%), acute dialyser reactions occurred, virtually always during the first exposure. Only two patients (case 16 & 18) could be treated successfully with an alternative PSu/PESu

Table 1. *Summary of cases of acute dialyser reactions reported in the literature between 2003 and 2016*

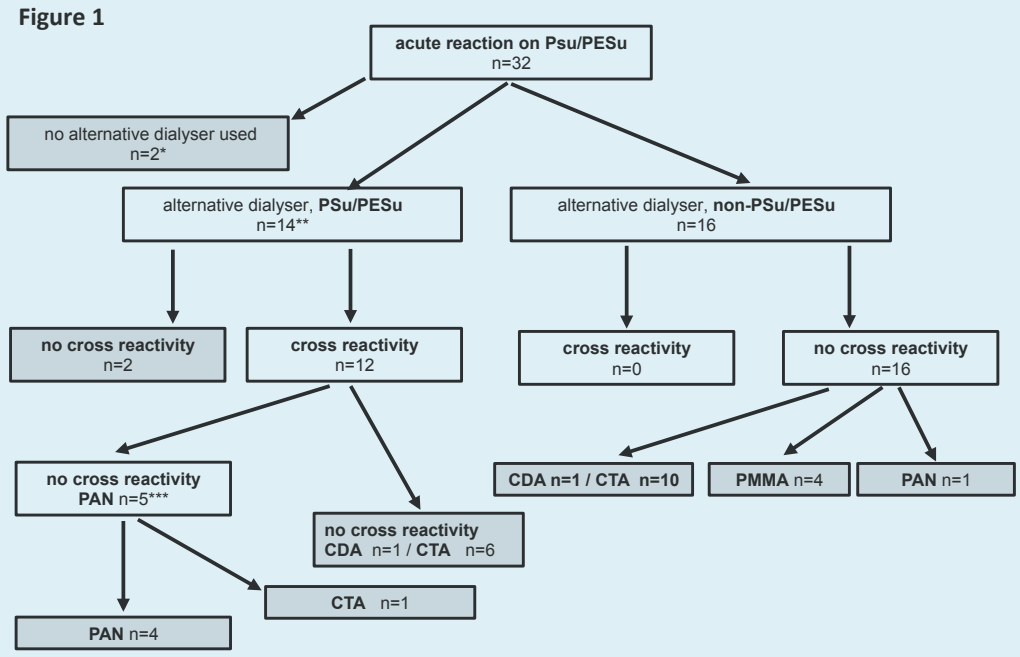
Case	Gender /age	Dialyser causing symptoms	Duration of exposure to dialyser	Alternative dialyser symptomatic	Alternative dialyser asymptomatic	Reference
1	F / 57	F8-HPS [a] (Fresenius) *polysulfone*	21 months	BS 1.8U (Toray) *polysulfone/*1st exposure	FB-170U (Nipro) *cellulose triacetate*	Ohashi (2003)[14]
2	F / 75	Optiflux F160Nre (Fresenius) *polysulfone*	1st exposure	Hemoflow F70Nre (Fresenius) *polysulfone/*1st exposure	Nephral ST400 [b] (Gambro) *PAN*	Yang (2005)[19]
3	M / 45	F10-HPS [c] (Fresenius) *polysulfone*	~3 years	-	Brand & type unspecified *Cellulose triacetate* [d]	Arenas (2006)[4]
4	M / 51	F8 [e] (Fresenius) *polysulfone*	1st exposure	F10-HPS (Fresenius) *polysulfone/*1st exposure	Brand & type unspecified *Cellulose triacetate* [f]	Arenas (2007)[5]
				180 MHP (Idemsa) *polyethersulfone/* 1st exposure		
5	F / 67	F-10-HPS [g] (Fresenius) *polysulfone*	1st exposure	-	Dicea 170 (Baxter) *cellulose diacetate*	Huang (2007)[9]
6	F / 84	FX-80 (Fresenius) *polysulfone*	1st exposure, ongoing for 1 month	Polyflux 17L (Gambro) [h] *Poly(aryl)ethersulfone/* 1st exposure	Nephral ST 500 (Gambro) *PAN*	Coentrão (2010)[7]
				BLS 512 (Bellco-Sorin) *polyethersulfone/* 1st exposure		
				FX-10 (Fresenius) *polysulfone/*1st exposure		
7	M / 77	Diacap PS15-PVP (Bbraun) *polysulfone*	10th & 11th session	FX-80 (Fresenius) *polysulfone/*1st exposure	Dicea 110G (Baxter) *cellulose diacetate*	Bacelar Marques (2011)[6]
8	F / 51	Optiflux F180NR (Fresenius) *polysulfone*	~2 years	-	CT-190G (Baxter) *cellulose triacetate*	Posadas (2011)[15]
					AM-BIO-100 (Asahi) *alkyl ether polymer grafted cellulose*	
9	F / 77	Toraylight CS-1.3U (Toray) *polysulfone*	2.3 months	-	FB-130Pβ (Nipro) *cellulose triacetate*	Konishi (2011)[10]
10	M / 79	PS-1.3UW (Fresenius) *polysulfone*	1 month	-	Filtryzer BG-1.3PQ (Toray) *PMMA*	
11	F / 75	Toraylight CS-1.3U (Toray) *polysulfone*	7.4 months	-	Filtryzer BG-1.3PQ (Toray) *PMMA*	
12	F / 64	PS-1.3UW (Fresenius) *polysulfone*	1st exposure	-	FB-130Pβ (Nipro) *cellulose triacetate*	
13	F / 63	Toraylight CS-1.3U (Toray) *polysulfone*	2-3 weeks	-	Filtryzer BG-1.3PQ (Toray) *PMMA*	
14	M / 65	PS-1.6UW (Fresenius) *polysulfone*	5 weeks	-	Filtryzer BG-1.6PQ (Toray) *PMMA*	

Case	Gender /age	Dialyser causing symptoms	Duration of exposure to dialyser	Alternative dialyser symptomatic	Alternative dialyser asymptomatic	Reference
15	M / 76	PS-1.3UW (Fresenius) *polysulfone*	5 weeks	FDX-150GW (Nikkiso) [i] *PEPA*/1st exposure	Filtryzer BG-1.3PQ (Toray) *PMMA* FB-150Pβ (Nipro) *cellulose triacetate*	
16	F / 34	Pureflux Purema (Nipro) *polyethersulfone*	1st and 2nd exposure	-	Prismaflex (Gambro) *Poly(aryl)ethersulfone*	Heegard (2013)[8]
17	M / 86	Polyflux 21H (=210H?) (Gambro) *Poly(aryl)ethersulfone*	4-6 weeks	FX-80M (Fresenius) *polysulfone*/1st exposure	Nephral [j] (Gambro) *PAN*	Martin-Navarro (2014)[11]
				BG 2.1U (Toray) *PMMA*/1st exposure	Sureflux 19UX (Nipro) *cellulose triacetate*	
18	F / 75	FX-60 [k] (Fresenius) *polysulfone*	2nd exposure	-	F6-HPS (Fresenius) *polysulfon*[e]	Shu (2014)[17]
19	M / 70	Rexeed [l] (Asahi) *polysulfone*	1st exposure	-	Patient died	Tsang (2014)[18]
20	M / 58	Polyflux 210H [m] (Gambro) *Poly(aryl)ethersulfone*	1st exposure	Elisio 21H (Nipro) *polyethersulfone*/ 1st exposure	Sureflux 21UX (Nipro) *cellulose triacetate*	Sanchez-Villanueva (2014)[16]
21	F / 80	Helixone FX-80 (Fresenius) *polysulfone*	~4 months and 1 month later	Polyflux 210H (Gambro) *Poly(aryl)ethersulfone*/ 3rd exposure	Sureflux 21UX (Nipro) *cellulose triacetate*	
				Elisio 21H (Nipro) *polyethersulfone*/after 8 months exposure		
22	M / 75	Helixone FX-100 Classix (Fresenius) *polysulfone*	1st exposure	FX-100 (Fresenius) *polysulfone*/1st exposure	Sureflux 21UX (Nipro) *cellulose triacetate*	
23	M / 48	Helixone FX-100 Classix (Fresenius) *polysulfone*	1st exposure	-	Lost to follow-up	
24	M / 70	Helixone FX-100 Classix (Fresenius) *polysulfone*	1st exposure [n]	-	Sureflux 21UX (Nipro) *cellulose triacetate*	
25	F / 83	Helixone FX-100 Classix (Fresenius) *polysulfone*	1st exposure	-	Sureflux 21UX *cellulose triacetate*	
26	M / 75	Polyflux H (Gambro) *Poly(aryl)thersulfone*	1st exposure [o]	-	Nephral ST (Gambro) *PAN*	Mazarakis (2014)[12]
27	M / 79	Optiflux F160 NR (Fresenius) *polysulfone*	2 years	-	Exceltra 150 (Baxter) *cellulose triacetate*	Mukaya (2015)[13]
28	M / 90	F8-HPS (Fresenius) *Polysulfone*	1st exposure	Polyflux 17L (Gambro) *Poly(aryl)ethersulfone*/ 1st exposure	Nephral ST 500 (Gambro) *PAN*	Cerqueira (2015)[2]
29	M / 69	Cordiax FX 600 [p] (Fresenius) *polysulfone*	32 months / 1st exposure	Polyflux 17L (Gambro) *Poly(aryl)ethersulfone*/ 1st exposure	Nephral ST 500 (Gambro) *PAN*	
30	F / 58	Optiflux F160Nre [q] (Fresenius) *polysulfon*	1st exposure	-	CT-110G (Baxter) *cellulose triacetate*	Sayeed (2015)[3]

Case	Gender /age	Dialyser causing symptoms	Duration of exposure to dialyser	Alternative dialyser symptomatic	Alternative dialyser asymptomatic	Reference
31	M / 74	F8-HPS (Fresenius) *polysulfone*	7 months	-	Sureflux 150-L (Nipro) *cellulose triacetate*	Current paper
32	M / 69	F8-HPS (Fresenius) *polysulfone*	3rd exposure	-	Sureflux 150-L (Nipro) *cellulose triacetate*	

M = male; F = female; PAN = polyacrylonitrile, PMMA = polymethylmethacrylate
[a] First episode on F8-HPS, attributed to bradycardia induced by β-blocker; nevertheless, dialysis continued using cellulose triacetate membrane; 2-3 weeks later switch to polysulfone (BS 1.8U), immediate dialyser reaction.
[b] Reaction to Nephral ST400 at second exposure, thereafter asymptomatic with double rinsing.
[c] From 1988 long-lasting exposure to various EtO-sterilised dialysers (cuprammonium, PAN, cellulose, polysulfone, PMMA) with dialysis reactions in 1988 and 1996.
[d] Type of cellulose triacetate dialyser not specified; symptomatic again after 12 sessions, followed by 23 uneventful sessions after which severe dialyser reaction, the patient died.
[e] Upon switch from cellulose diacetate dialyser (type not specified, gamma sterilisation) that did not cause reactions to the F8 polysulfone dialyser.
[f] Types of dialyser not specified.
[g] Eleven years on Dicea 210G, out of stock, switch to F10-HPS. Intubation and severe laryngeal oedema 2 hours into dialysis.
[h] Mixture of polyarylethersulfone, polyvinylpyrrolidone and polyamide.
[i] Polyester-polymer alloy.
[j] After 1 month continuous urticaria and eosinophilia, no acute dialyser reactions, change to FX 80M (acute reaction), continued on Nephral, 12 months later switched to Sureflux 19UX because of ongoing urticaria and eosinophilia; 3 months later trial BG 2.1U (PMMA, acute reaction), continued on Sureflux 19UX.
[k] Treated with F6-HPS two weeks before (2 sessions) without problems.
[l] Specific type of Rexeed dialyser not mentioned, unknown duration and number of preceding treatments with Revaclear (polyarylethersulfone, polyvinylpyrrolidone / steam).
[m] More then one year uneventful on Helixone FX-800 (polysulfone), change to Polyflux 210H because of supply problems.
[n] Preceding exposure to Aquamax HF12 haemofilter (polyethersulfone, ethylene oxide sterilisation) while in resuscitation unit.
[o] Regular haemodialysis treatment on Nephral ST dialyser for 3 years; because of unavailability of this dialyser single dialysis using Polyflux H dialyser with acute reaction within 10 minutes. Return to Nephral-ST dialyser without further problems (personal communication, N.G. Kounis).
[p] Same dialyser used 32 months in USA, first dialysis with same dialyser in Portugal acute reaction.
[q] Four years on cellulose triacetate dialyser (CT-110G) in patients own outpatient centre, switched to Optiflux F160Nre* during hospital admission.

Figure 1. *Flow diagram showing the effect of switching to either PSu/PESu or non PSu/PESu alternative dialysers*



PSu/PESu = polysulfone/polyethersulfone; CDA = cellulose diacetate; CTA = cellulose triacetate; PAN = polyacrylonitrile; PMMA = polymethylmethacrylate. *one patient died, one lost to follow-up; **11 patients challenged with 1 alternative PSu/PESu dialyser, 2 patients with 2 different PSu/PESu dialysers, 1 patient with 3 different PSu/PESu dialysers (total of 18 trials); ***patient 17 later switched from PAN to CTA because of pruritus / urticaria.

containing dialyser.[8,17] Cross-reactivity between PSu/PESu dialysers was extensive, both within membrane type (PSu vs. PSu or PESu vs. PESu, respectively), between membrane types (PSu vs. PESu) and within and between brands (*table 1*).

Figure 1 shows that of the 12 patients that showed cross-reactivity to a PSu/PESu dialyser, eight (66.7%) were eventually treated without problems with a dialyser containing modified cellulose, and four switched successfully to a PAN dialyser. Of the 16 patients that were not rechallenged with an alternative PSu/PESu dialyser, 11 reacted favourably to substituted cellulose, four to a dialyser containing a polymethylmethacrylate (PMMA) membrane and one patient returned to the PAN containing dialyser he had used previously.

Table 2A summarises the PSu/PESu containing dialysers (n = 20) that caused the initial acute dialyser reactions (n = 32) as well as the cross-reactions (n = 16). They differed in sterilisation method, housing material and hydraulic permeability. For instance, steam (35%), gamma radiation (45%) and electron beam sterilisation (10%) were all applied. Polycarbonate and polypropylene were used as housing materials, and both high flux (13/20, 65%) and low flux (6/20, 30%) dialysers are listed. All dialysers contained polyurethane as a potting substance, but this material was also used in all non-PSu/PESu dialysers that did not cause acute dialyser reactions in patients reacting to PSu/PESu (*table 2B*).

Table 2B lists the non-PSu/PESu dialysers that could be used safely in patients reacting to PSu/PESu membranes. With regard to the sterilisation method, housing and potting material and hydraulic permeability characteristics, they overlap with the PSu/PESu dialysers in *table 2A*. The only conspicuous distinguishing feature is the difference in membrane materials.

DISCUSSION

We report two patients with acute dialyser reactions that occurred when using a PSu dialyser. They became asymptomatic after switching to a CTA dialyser. Supporting the notion that the dialyser reactions were caused by the PSu membrane, both patients immediately developed symptoms after intentional (patient 1) and accidental (patient 2) rechallenge with the PSu dialyser.

Thirty additional cases of acute dialyser reactions were found in the literature dating from the beginning of the current century,[2-19] an era in which the use of biocompatible, non-EtO sterilised dialysers has become standard practice. The reactions usually occur within the first 30 minutes of dialysis, are characterised by severe cardiopulmonary symptoms and fit the diagnostic criteria of anaphylaxis.[21] Interestingly, acute dialyser reactions occurred shortly after the initial exposure to the offending dialyser in only half of the reports, the average delay being almost a year in the remaining cases.

All reactions were caused by dialysers that contained a polyarylsulfonate membrane, which includes PSu and polyethersulfone (PESu).[20] About half of the patients were re-exposed to a PSu/PESu dialyser that differed from the original offending PSu/PESu dialyser. Repeat acute reactions occurred in 85% of them, forcing a switch to a non-PSu/PESu dialyser. The remainder of the patients were not exposed to a different PSu/PESu dialyser but switched directly to a non-PSu/PESu dialyser. Overall, of the patients reacting to PSu/PESu dialysers that had follow-up (n = 30), two were continued on an alternative PSu/PESu dialyser. The vast majority were switched to non-PSu/PESu dialysers, including modified cellulose dialysers (n = 19, mainly CTA), a PAN dialyser (n = 5) or a PMMA dialyser (n = 4).

PSu/PESu dialysers that provoked acute reactions differed in hydraulic permeability, sterilisation method and housing material. All contained polyurethane as potting material, but this was also the case for the non-PSu/PESu dialysers shown to be safe in patients reacting to PSu/PESu. This leaves the membrane material as the only recognisable common factor (*table 2A*). In the patients that were rechallenged with an alternative PSu/PESu dialyser, cross-reactivity was extensive, within membrane type (PSu vs. PSu or PESu vs. PESu), between membrane types (PSu vs. PESu) and within and between brands (*table 1*). Neither the various PSu nor the different PESu containing dialysers are identical products, as the capillary walls may differ in thickness, geometry, layering and luminal smoothness as well as in pore size and pore size distribution.[22] This suggests that an essential determinant of the basic PSu and PESu polymers causes the acute reactions.

One explanation for the finding that PSu/PESu dialysers caused all reported initial dialyser reactions could be that approximately 93% of dialysers currently used contain PSu/PESu,[23] leading to exposure of many more patients to these dialysers than to those containing CTA, PAN or PMMA. However, recent research also suggests that PSu and CTA dialysers differ in biocompatibility. Dialyser protein adsorption patterns differ in asymptomatic dialysis patients exposed to a PSu and CTA dialyser in that the former, but not the latter, adsorbed ficolin-2, a substance that may directly activate the complement system via the lectin pathway.[24] A similar study suggested that CTA was more biocompatible than PSu in terms of activation of the coagulation cascade.[25] In agreement with this, a PSu membrane, but not a CTA membrane, caused a substantial increase in indicators of platelet activation in asymptomatic dialysis patients[26] or patients with acute renal failure treated by continuous venovenous haemofiltration.[27] Consistent with this, dialysis-induced thrombocytopenia

Table 2. *A: Polysulfone and polyethersulfone (PSu/PESu) dialysers causing acute reactions at the initial reaction and after exposure to alternative dialysers from this family; B: Dialysers that could be used safely in patients reacting to PSu/PESu dialysers*

A: Dialysers causing acute reactions	Manufacturer	Membrane material	Manufacturer designation	Sterilisation	Housing material	Potting material	HF/LF	No. of reactions	Reference
Polyflux H series	Gambro	poly(aryl) ethersulfone	Polyamix™	Steam	Polycarbonate	Polyurethane	HF	4	11,12,16
Polyflux L series	Gambro	poly(aryl) ethersulfone	Polyamix™	Steam	Polycarbonate	Polyurethane	LF	3	2,7
PS UW series (1.3UW, 1.6UW)	Fresenius	Polysulfone	-	?	?	?	?	4	10
F-8	Fresenius	Polysulfone	Fresenius Polysulfone®	EtO	Polycarbonate	Polyurethane	LF	1	5
F-HPS series (HPS-8, HPS-10)	Fresenius	Polysulfone	Fresenius Polysulfone®	Steam	Polycarbonate	Polyurethane	LF	7	2,4,5,9,14, this paper
Hemoflow F70NR	Fresenius	Polysulfone	Fresenius Polysulfone®	Electron beam	Polycarbonate	Polyurethane	HF	1	19
Optiflux NR (F160, F180)	Fresenius	Polysulfone	Advanced Fresenius Polysulfone Optiflux®	Electron beam	Polycarbonate	Polyurethane	HF	4	3,13,15,19
FX series (low flux, FX-10)	Fresenius	Polysulfone	Helixone®	Steam	Polypropylene	Polyurethane	LF	1	7
FX series (high flux, FX-60, FX-80, FX-100)	Fresenius	Polysulfone	Helixone®	Steam	Polypropylene	Polyurethane	HF	6	6,7,11,16,17
FX-Classix series (FX-Classix 100)	Fresenius	Polysulfone	Helixone®	Steam	Polypropylene	Polyurethane	HF	4	16
Cordiax FX (FX600)	Fresenius	Polysulfone	Helixone® plus	Steam	Polypropylene	Polyurethane	HF	1	2
Diacap LO PS15	Bbraun	Polysulfone	Diacap® α	Gamma radiation	Polycarbonate	Polyurethane	LF	1	6
FDX series (150GW)	Nikkisso	Polyether-sulfone and polyarylate	PEPA®	Gamma radiation	Polycarbonate	Polyurethane	HF	1	10
Elisio 21H	Nipro	Polyether-sulfone	Polynephron™	Gamma radiation	Polypropylene	Polyurethane	HF	2	16
Pureflux, type not specified	Nipro	Polyether-sulfone	Purema®	Gamma radiation	Polycarbonate	Polyurethane	HF (?)	1	8
BG TS-U series (1.8U)	Toray	Polysulfone	Toraysulfone®	Gamma radiation	Polycarbonate	Polyurethane	HF	1	2
Toraylight CS series (1.3U)	Toray	Polysulfone	-	Gamma radiation	Polypropylene	Polyurethane	HF	3	10
BLS 512	Bellco-Sorin	Polyether-sulfone	?	Gamma or steam	?	?	LF	1	7
Rexeed, type not specified	Asahi	Polysulfone	Rexbrane™	Gamma radiation	?	?	HF	1	18
180 MHP	Idemsa	Polyether-sulfone	?	Gamma radiation	?	?	HF	1	5

B: Safe alternative dialysers*	Manu-facturer	Membrane	Manufacturer designation	Sterili-sation	Housing material	Potting material	HF/LF	No. of reports	Reference
Dicea series (110G, 170G)	Baxter	Cellulose diacetate	n.a.	Gamma radiation	Polycarbonate	Polyurethane	LF	2	6,9
CT-series (110G, 190G)	Baxter	Cellulose triacetate	n.a.	Gamma radiation	Polycarbonate	Polyurethane	HF	2	3, 15
Exeltra 150	Baxter	Cellulose triacetate	n.a.	Gamma radiation	Polycarbonate	Polyurethane	HF	1	13
FB series (170U, 130P β, 150 P β)	Nipro	Cellulose triacetate	n.a.	Gamma radiation	Polypropylene	Polyurethane	HF	4	10, 14
Sureflux (19UX, 21UX)	Nipro	Cellulose triacetate	n.a.	Gamma radiation	Polypropylene	Polyurethane	HF	6	11,16
Sureflux (150L)	Nipro	Cellulose triacetate	n.a.	Gamma radiation	Polypropylene	Polyurethane	LF	2	This paper
AM-BIO-100	Asahi	Alkyl ether polymer grafted cellulose	n.a.	Gamma radiation	?	?	?	1	15
Nephral ST (ST400, ST500, not specified)	Gambro	Polyacryloni-trile	n.a.	Gamma radiation	Polycarbonate	Polyurethane	HF	6	2,7,11,12,19
Filtryzer BG series (1.3 PQ, 1.6 PQ)	Toray	Polymethyl-methacrylate	Filtryzer®	Gamma radiation	Polystyrene	Polyurethane	HF	5	10

*Two patients were treated successfully with a cellulose triacetate dialyser that was not further specified (reference 4 and 5). HF / LF = high flux /low flux; n.a.= not applicable.

provoked by a PSu dialyser resolves after switching to a CTA (or PAN) dialyser.[28,29] These observations suggest that PSu dialysers confer an increased risk of acute reactions compared with those containing CTA. Unfortunately, PAN and PMMA dialysers have not been compared directly with those containing PSu or CTA using the same analytical methods.

Our observations suggest that the dialysers containing modified cellulose, PAN and PMMA shown in *table 2B* can be used unreservedly in patients reacting to PSu/PESu dialysers. However, this protective effect may not be complete and acute reactions are not restricted entirely to PSu/PESu dialysers. Patient 3 reacted to a PSu dialyser and switched successfully to a CTA dialyser, only to develop acute reactions several weeks later. Patient 17 reacted to a PESu and a PSu dialyser, but also to a PMMA dialyser. A PAN dialyser caused urticaria and eosinophilia necessitating a switch to a CTA membrane. Hanada et al. reported a patient reacting from his first dialysis to dialysers containing CTA, PSu, vitamin E coated PSu, PMMA, polyester polymer alloy and ethylene vinyl alcohol copolymer (EVAL) who could only be dialysed using a CTA dialyser combined with temporary corticosteroids.[30] Quinones et al. reported a patient having acute reactions to both a PSu dialyser and one containing EVAL.[31] Consequently, some patients also appear to be prone to anaphylactic reactions to dialyser membranes other than PSu/PESu, suggesting an important interaction between membrane biocompatibility and patient-related factors. Indeed, the severity of anaphylactic reactions can be affected by co-factors, both patient specific and non-specific.[32] The latter include infections, common in patients on dialysis, and drugs often used by dialysis patients such as acetylsalicylic acid, β-blockers and ACE inhibitors.[33] Interestingly, although the detrimental effects of ACE inhibitors were specifically linked to PAN membranes,[34] the patient described by Quinones et al. only had acute reactions to both the PSu and the EVAL dialyser during ACE inhibition.[31] Consequently, it is worthwhile to pay attention to potential modifiable factors in patients reacting to dialysers.

It is of note that eight cases of acute reactions to surface-treated PAN dialysers (Nephral-ST) have been reported in patients on ACE inhibitors.[35-38] Reactions to dialysers containing the original PAN membranes with their very negatively charged, bradykinin-inducing surface have been reported in patients on ACE inhibitors.[34] Membrane surface treatment with polyethyleneimine was

used to reduce membrane electronegativity and prevent this complication.[39] However, no cases of a reaction to a Nephral-ST dialyser, attributed to incomplete PEI coating, have been reported after 2007.[38]

The number of patients on haemodialysis throughout the world has increased from approximately 1.5 to 2.5 million in the past decade.[40] Consequently, hundreds of millions of dialysers are being used annually, the vast majority of which contain PSu/PESu. With only 32 contemporaneous reported cases of acute reactions to PSu/PESu dialysers, their verified incidence is extremely low, although underreporting is likely. Interestingly, 85% of the cases summarised in this paper were reported in or beyond 2010, suggesting an increasing trend. This rise could be related to increased awareness or reflect the increasing number of patients being treated. However, it is also possible that ongoing modifications to the original PSu membrane developed in the early 1980s,[41] aimed at enhancing dialyser performance, may also negatively affect dialyser biocompatibility. In this context, the Urgent Field Safety Notice issued by Fresenius in 2015 for the new line of FX CorDiax High-Flux dialysers and haemodiafilters (PSu, Helixone®) may be relevant,[42] as this notice was spurred by *'an increased number of cases of hypersensitivity and hypersensitivity-like reactions with the application of the FX CorDiax dialysers, including life-threatening events during continuous post market surveillance'*.

Although rare, acute dialyser reactions are not a thing of the past and dialysis staff should be aware of them as the incidence may be increasing. They should be considered in patients on haemodialysis using PSu/PESu dialysers who develop cardiopulmonary signs and symptoms in the early phase of dialysis sessions for which no alternative explanation is readily available. These include cardiac failure or ischaemia, arrhythmia, ultrafiltration-related dialysis hypotension or allergic reactions to drugs that are given intravenously prior to dialysis. As ~85% of patients reacting to a PSu/PESu containing dialyser will also react to other dialysers of the same family, we suggest that they should not be challenged with alternative PSu/PESu dialysers if the diagnosis is suspected. It seems advisable to switch them directly to a non-PSu/PESu dialyser, which should immediately and consistently lead to disappearance of symptoms. Most experience is available with CTA dialysers, but alternatives include those containing PAN or PMMA.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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ORIGINAL ARTICLE

Validation of the 1 µg short synacthen test: an assessment of morning cortisol cut-off values and other predictors

F.T. Perton[1]*, G.S. Mijnhout[1], B.J. Kollen[2], J.M.M. Rondeel[3], A.A.M. Franken[1], P.H.P. Groeneveld[1]

[1]Department of Internal Medicine, Isala, Zwolle, the Netherlands, [2]Department of General Practice, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands, [3]Department of Clinical Chemistry, Isala, Zwolle, the Netherlands, *corresponding author: tel.: +31 (0)38-4243350, e-mail: f.perton@isala.nl

ABSTRACT

Background: Clinical practice shows that many low-dose short synacthen tests (LD-SSTs) for diagnosing adrenal insufficiency in an outpatient setting have a normal outcome and could be considered superfluous. The objective of this study is to provide a guideline to safely reduce the number of unnecessarily performed LD-SSTs.
Methods: Data of LD-SSTs performed in outpatients were collected. Optimal morning cortisol cut-off values were determined using ROC analysis. Subsequently the predictive value of several variables was tested using univariable and multivariable logistic regression analyses.
Results: A morning cortisol lower cut-off value of 145 nmol/l (specificity 89.9%, positive predictive value 90.0%) and an upper cut-off value of 375 nmol/l (sensitivity 100.0%, negative predictive value 100.0%) were found. Chronic fatigue symptoms and symptoms of hypotension or orthostasis as the main reason for performing the test predict a normal outcome. The use of glucocorticosteroids predicts an abnormal outcome of the LD-SST. Oral, topical, nasal and inhaled glucocorticosteroids are each significant predictors when analysed specifically for predicting central adrenal insufficiency.
Conclusion: By using morning cortisol cut-off values of 145 nmol/l and 375 nmol/l instead of the conventional cut-off values, the number of LD-SSTs performed in an outpatient setting can be reduced by 12%, while maintaining high sensitivity and specificity. Furthermore, the outcome of the LD-SST can be predicted by additional variables such as the indication for performing the test and the use of glucocorticosteroids. Different routes of administration of glucocorticosteroids such as inhalation or topical use should be taken into account when central insufficiency is suspected.

KEYWORDS

ACTH stimulation test, adrenal insufficiency, low dose synacthen test, morning cortisol

INTRODUCTION

The measurement of serum morning cortisol concentration is an appropriate and practical first-line screening test for adrenal insufficiency.[1] Upper and lower cortisol cut-off values are used to differentiate between low levels (where adrenal insufficiency can be diagnosed without further dynamic hypothalamic-pituitary-adrenal (HPA) axis testing), intermediate levels (where dynamic testing is needed to confirm or reject the diagnosis), and high levels (where the diagnosis can be safely rejected without additional testing).
Several factors influence the interpretation of the serum cortisol level. Firstly, most assays that are used for determining the serum cortisol concentration measure the total cortisol concentration. This consists of the concentrations of free cortisol, cortisol bound to corticosteroid-binding globulin (CBG) and cortisol bound to albumin.[2,3] Because of this, elevated concentrations can be found when CBG is increased by oestrogen therapy, or decreased concentrations can be found when CBG is reduced in liver diseases such as cirrhosis.[4,5] Furthermore, the measured cortisol level varies between different cortisol assays, making it difficult to set morning cortisol cut-off values that can be generally applied.[4,6]
The generally accepted lower and upper cut-off values of morning cortisol are 100 nmol/l and 500 nmol/l, respectively.[1,7] However, reported lower cortisol cut-off values range from 80 nmol/l to 165 nmol/l and reported

upper morning cortisol levels range from 236 nmol/l to 500 nmol/l.[7-20] This variability may in part be due to the difference in the cortisol assays used. Also, these reported values are defined by their sensitivity and specificity to predict the outcome of different dynamic ACTH tests. In most studies reporting morning cortisol criteria, the cut-off values are related to the outcome of the insulin tolerance test. In newer studies, the cut-off values are related to the high-dose (250 µg) short synacthen test. Interestingly, we could not find reported morning cortisol cut-off values directly related to the outcome of the low-dose (1 µg) short synacthen test (LD-SST).

Multiple meta-analyses have been performed comparing high- and low-dose ACTH stimulation tests.[21-23] Two meta-analyses report similar diagnostic performance of the two tests and one reports a better performance of the low-dose test. Several studies have shown that the LD-SST is more sensitive for diagnosing mild or recent-onset central adrenal insufficiency.[24-35]

The LD-SST is a suitable and frequently used dynamic test for diagnosing adrenal insufficiency. Nevertheless morning cortisol cut-off values related to the LD-SST are lacking. The aim of this study is to provide these cut-off values and to identify other variables that can be used to predict the outcome of the LD-SST.

MATERIALS AND METHODS

Patients

Data of all patients who underwent an outpatient LD-SST in our hospital from January 2003 to March 2015 were collected retrospectively. Only the first LD-SST in this period was included when more than one test was performed per patient. All tests of which a morning cortisol measurement up to three months prior to the LD-SST was known were identified. Morning levels were defined as samples taken between 7:00 and 9:00 am. According to protocol, glucocorticosteroids must be discontinued at least 24 hours prior to the LD-SST. However, due to the retrospective nature of this study it cannot be ascertained that all patients were thus instructed by their referring physician.

Materials and definitions

LD-SSTs were carried out between 8:00 am and 17:00 pm. All tests were performed by a small group of well-trained medical personnel. Patients received an indwelling intravenous catheter. At t = 0 a venous blood sample was taken. Subsequently a 1 µg bolus of synthetic $ACTH_{1-24}$ (Synacthen®) was administered intravenously. The 1 µg solution was freshly prepared by diluting a 250 µg ampoule of tetracosactide (Novartis Pharma, Nurnberg, Germany) in normal saline (final volume 0.5 ml). The syringe was flushed with 1 ml of normal saline to ensure complete intravenous injection of the 1 µg solution. After 30 minutes venous blood samples were taken for cortisol measurement. The outcome of the LD-SST was considered normal if cortisol levels at either t = 0, t = 30 or t = 60 were higher than 500 nmol/l. The outcome of the test was considered abnormal if cortisol levels were below 500 nmol/l in all samples.

Hormone analysis

All serum cortisol samples were analysed in a solid-phase competitive chemiluminescence enzyme immunoassay using the Immulite 2000 platform (Siemens Medical Solutions Diagnostics, Los Angeles, CA). The intra- and inter-assay coefficients of variation of the cortisol assay are < 10%.

Data collection and definitions

For each patient, morning cortisol concentration prior to the test (if known), use of glucocorticosteroids, history of autoimmune diseases and the main reason for performing the LD-SST were recorded. These reasons were divided into five categories: chronic fatigue symptoms, chronic fatigue in combination with a history of thyroid disease, symptoms of orthostasis or hypotension, suspected pituitary pathology and all other reasons. Only autoimmune diseases associated with autoimmune polyglandular syndrome (APS) type 1, 2 and 4 in the patient history were recorded: diabetes mellitus type 1, hypoparathyroidism, mucocutaneous candidiasis, pernicious anaemia, hypothyroidism, Graves' disease, Hashimoto's thyroiditis, coeliac disease, primary hypogonadism, alopecia, vitiligo, autoimmune hepatitis and chronic gastritis.[36] Additionally, pregnancy or oestrogen therapy during testing and history of liver diseases were recorded. Also the final diagnosis as documented by the physician after interpretation of the LD-SST and any additional tests was recorded.

Statistical analysis

For determining upper and lower morning cortisol cut-off values, receiver operator characteristic (ROC) curve analysis was performed. The predictive value of the different predictor variables was tested by univariable and multivariable binary logistic regressions. Firstly, all the predictor variables were analysed using univariable binary regression models. Subsequently, all predictors with a p-value higher than 0.200 were included in a multivariable binary regression model. Stepwise, the predictor with the highest p-value was excluded from the model until the model consisted of only statistically significant predictors, $p < 0.05$. We adhered to the 'events per variable' rule to ensure adequate power in the logistic regression analyses.[37] All statistical analyses were performed with SPSS version 22 for Windows.

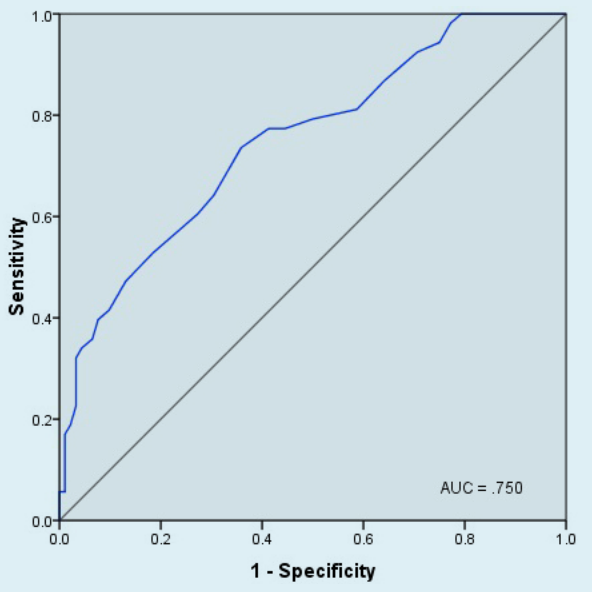
RESULTS

Morning cortisol cut-off values

For determining optimal upper and lower cortisol cut-off values, a ROC curve was used (*figure 1*). Including only the outpatient LD-SSTs of which a morning cortisol level prior to the test was known, 145 tests and corresponding morning cortisol measurements were analysed. The area under the curve was 0.750 (95% CI 0.66-0.832, p = 0.000). The optimal lower cut-off value of morning cortisol was set at a point that ensured identification of all abnormal LD-SSTs, having the highest specificity and the highest positive predictive value. The optimal upper morning cortisol value was set at a point that ensured identification of all normal LD-SSTs, having the highest sensitivity and the highest negative predictive value (*table 1*).

In this sample there was one patient with an immeasurably low morning cortisol level and nonetheless a normal LD-SST. This low morning cortisol level was possibly due to a measurement error. Also, the basal cortisol measurement in the LD-SST of this patient (performed at 9:20 am) was 310 nmol/l. The optimal lower cut-off value of morning cortisol was set at 145 nmol/l. If the data of this one patient were included in the analysis, the specificity and positive predictive values were 89.9% and 90.0%, respectively. If this patient was excluded from the analysis, however, both specificity and positive predictive value were 100%. The optimal upper cut-off value was set at 375 nmol/l, with 100% sensitivity and 100% negative predictive value.

Figure 1. *ROC curve of morning serum cortisol predicting an abnormal outcome of the LD-SST*



AUC = area under the curve, p < 0.01, 95% confidence interval 0.667-0.832.

OTHER PREDICTOR VARIABLES OF THE LD-SST

A prediction model was fitted using univariable and multivariable binary logistic regression analysis of the defined predictor variables. Due to the small number of patients in this sample group, only two variables other than morning cortisol concentration could be included in a statistically significant prediction model.

The number of analysed tests was increased by also including the LD-SSTs without a morning cortisol measurement prior to the test. All LD-SSTs performed in an outpatient setting from January 2010 to March 2015 were analysed, resulting in a sample of 329 patients. Patient demographics are summarised in *table 2*. The average age was 47 years. There was no significant difference between the ages of patients with a normal or an abnormal outcome of the LD-SST (Mann-Whitney test, p = 0.154). A total of 76 tests (23.1%) were abnormal.

The final prediction model of the LD-SST showed a significant predictive value of a history of autoimmune diseases associated with APS, use of glucocorticosteroids, fatigue symptoms and symptoms of hypotension (*table 3*). Notably, 39.5% of the 38 patients that used glucocorticosteroids had an abnormal LD-SST.

Predictors of central adrenal insufficiency

As shown in *table 2*, nearly half of the patients with abnormal LD-SSTs are ultimately diagnosed with central adrenal insufficiency and only 14.5% of patients with abnormal tests are diagnosed with primary adrenal insufficiency. We hypothesised that the use of glucocorticosteroids would be a

Table 1. *Morning cortisol cut-off values*

Morning cortisol	True positive	True negative	False positive	False negative	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
145 nmol/l	9	91	1	44	17.0	89.9	67.4	90.0
375 nmol/l	53	19	73	0	100	20.7	100.0	42.0

NPV = negative predictive value, PPV = positive predictive value.

Table 2. *Patient demographics*

		Comorbidity	
Total sample size	329	Autoimmune disease associated with APS	58 (17.6%)
Average age (mean ± SD)	47.10 ± 4.650	Other autoimmune disease	9 (2.7)
Male	115 (35%)	Liver disease	12 (3.7%)
Female	214 (65%)	**Reason for performing LD-SST**	
Pregnant	2 (0.6%)	Fatigue symptoms	91 (27.7%)
Morning cortisol		Fatigue and thyroid disease	52 (15.8%)
Morning cortisol measured	204 (62%)	Hypotension/orthostasis	38 (11.6%)
Morning cortisol measured 7:00-9:00	80 (24.3%)	Pituitary pathology suspected	79 (24%)
Medication		Other	69 (21%)
Use of glucocorticosteroids	38 (11.6)	**Diagnosis**	
Oral glucocorticosteroids	8 (2.4%)	Abnormal LD-SST	76 (23.1%)
Inhalation glucocorticosteroids	12 (3.6%)	No adrenal insufficiency	276 (83.9%)
Nasal glucocorticosteroids	9 (2.7%)	Primary adrenal insufficiency	12 (3.6%)
Topical glucocorticosteroids	9 (2.7%)	Abnormal LD-SST and PAI	11 (3.3%)
Oestrogen therapy	26 (7.9%)	Central adrenal insufficiency	41 (12.5%)
Oestrogen therapy unknown	56 (17%)	Abnormal LD-SST and CAI	37 (11.2%)

APS = autoimmune polyglandular syndrome, LD-SST = low-dose short synacthen test, PAI = primary adrenal insufficiency, CAI = central adrenal insufficiency.

Table 3. *Multivariable binary logistic regression model for the LD-SST*

Variable	Odds ratio		95% CI	p-value
Autoimmune disease associated with APS	0.24		0.09 - 0.62	0.00
Use of glucocorticosteroids	2.69		1.25 - 5.75	0.01
Fatigue	0.42		0.22 - 0.81	0.01
Hypotension/orthostasis	0.16		0.04 - 0.54	0.00
Constant	0.46			0.00

APS = autoimmune polyglandular syndrome, CI = confidence incidence, Nagelkerke $R^2 = 0.137$, $\chi^2 = 31.185$, p = 0.000. Hosmer and Lemeshow p = 0.913.

stronger predictor when *a priori* central adrenal insufficiency is suspected. A second predictor model was fitted for predicting central adrenal insufficiency (*table 4*). Because only 12 patients were diagnosed with primary adrenal insufficiency, no multivariable predictor model for this diagnosis could be developed based on the ten events per predictor variable rule.

DISCUSSION

Morning cortisol cut-off values

Only a small number of LD-SSTs performed in an outpatient setting have an abnormal outcome. In our sample, only 23.1% of the tests were abnormal. We hypothesised that the number of unnecessarily performed tests could be safely reduced, primarily by determining morning cortisol cut-off levels specifically related to the LD-SST.

We could find no such cut-off values in the current literature, since all research done regarding morning cortisol and its relation to dynamic ACTH-axis testing is related to either the insulin tolerance test or the high-dose short synacthen test.[7-20] These data have been extrapolated to the LD-SST without supporting evidence in the literature.

Based on a ROC analysis of morning cortisol measurements in 145 subjects, a lower morning cortisol

Table 4. *Multivariable binary logistic regression model for central adrenal insufficiency*

Variable	Odds ratio		95% confidence interval	p-value
Use of glucocorticosteroids				0.00
Oral glucocorticosteroids	9.2		1.6 - 52.98	0.01
Inhalation glucocorticosteroids	6.75		1.57 - 28.98	0.01
Nasal glucocorticosteroids	24.13		5.44 - 107.1	0.00
Pituitary pathology suspected	13		5.67 - 29.81	0.00
Constant	0.03			0.00

Nagelkerke $R^2 = 0.322$, $\chi^2 = 61.348$, $p = 0.000$. Hosmer and Lemeshow $p = 0.594$.

concentration of 145 nmol/l and an upper morning cortisol concentration of 375 nmol/l were identified as optimal cut-off values using the Immulite 2000 cortisol assay. By using these new cut-off values instead of conventional cut-off values of 100 nmol/l and 500 nmol/, the number of justified LD-SSTs would be reduced by 12% based on our data sample.

OTHER PREDICTOR VARIABLES OF THE LD-SST

The second hypothesis was that other than only morning cortisol concentrations, additional predictors could be used to identify patients with an abnormal LD-SST. As expected, a normal outcome of the LD-SST was more likely when the main reason for performing the test was chronic fatigue or symptoms of orthostasis. When there are no other supportive arguments for adrenal insufficiency than these symptoms, performing the LD-SST should be reconsidered.

Also as hypothesised, the use of glucocorticosteroids predicted an abnormal outcome of the LD-SST. Chronic use of glucocorticosteroids is one of the most common causes of central adrenal insufficiency, other common causes being pituitary processes and iatrogenic causes after pituitary surgery or radiation therapy. A meta-analysis by Broersen et al. shows that development of adrenal insufficiency can occur in up to 60% of patients using glucocorticosteroids, depending on the route of administration, dosage and duration of use.[38]

In our study, 13% of 37 patients with an abnormal LD-SST who were diagnosed with central adrenal insufficiency used glucocorticosteroids. Most patients with central adrenal insufficiency had a pituitary tumour or pituitary surgery (59.5%). Other causes were Sheehan's syndrome (5.4%) or unknown (21.6%). These results underline that other than pituitary processes or surgery, glucocorticosteroid use is a common cause of central adrenal insufficiency.

On a side note, although glucocorticosteroid use was considered the cause of central adrenal insufficiency in a large number of patients, the chronic use of glucocorticosteroids in itself was rarely the reason for performing the LD-SST in our population. Fatigue symptoms and suspected pituitary pathology were the most common reasons for performing the test (*table 2*).

Analysis of different routes of administration of glucocorticosteroids in our study did not provide significant results. However, when analysed for predicting the final diagnosis of secondary adrenal insufficiency, the use of oral, inhalation and nasal glucocorticosteroids were all significant predictors. We therefore suggest that not only oral administration, but also inhalation and nasal administration of glucocorticosteroids can be used as a supportive argument for performing the LD-SST.

Inhaled glucocorticosteroids are known to have systemic steroid activity. A recent systemic review reports HPA suppression resulting in suppressed urinary cortisol, depending on the type of inhaled glucocorticosteroids used.[39] Multiple studies show no suppressing effect of nasal glucocorticosteroids on the HPA axis and dynamic stimulation tests, in a maximum treatment period of four weeks.[40,41] The effects of long-term use of nasal glucocorticosteroids on ACTH stimulation tests, however, remain unclear.

Three variables that might interfere with measured cortisol levels were also included in the analysis, namely pregnancy or oestrogen therapy during testing and a history of liver disease. None of these variables were significant predictors in the final model. Nevertheless, oestrogen therapy was a marginally significant predictor of the LD-SST when analysed using univariable binary logistic regression. Its predictive value might be stronger than we found, because in 26.2% of all females the use of oestrogen therapy during testing was unknown. This illustrates that often this variable is overlooked when diagnosing adrenal insufficiency.

In the literature, a two- to three-fold elevation of CBG concentration has been observed in women using oral

contraceptives, leading to concordantly elevated morning and stimulated cortisol levels in ACTH stimulation tests.[4] Although oestrogen therapy was not a significant addition to the final model in our study, it does appear to be an important factor. Oral contraceptives should be discontinued before the LD-SST is performed or specific cut-off levels should be used. Also, the use of oral contraceptives should be taken into account when interpreting a screening morning cortisol measurement.

Unexpected results

In the final predictive model for an abnormal LD-SST, a history of autoimmune diseases associated with APS predicted a normal outcome. This was the opposite of what was expected. We hypothesised that primary adrenal insufficiency and therefore an abnormal LD-SST would be more likely. This unexpected result could be explained by the relatively small number of patients with an abnormal LD-SST and final diagnosis of primary adrenal insufficiency in the sample group. In our sample group this was the case in only 3.3% of the subjects, compared with 11.2% of the subjects where the LD-SST was abnormal and central adrenal insufficiency was diagnosed. Autoimmune diseases are not associated with central adrenal insufficiency. Also the *a priori* chance of primary adrenal insufficiency is small, the incidence in Europe is 4.4-6.0 per million per year.[1] It could be that in patients with a history of APS-associated autoimmune disease, it is more likely that their symptoms have a different aetiology than adrenal insufficiency. It seems that such a patient history does not make an abnormal LD-SST more likely.

Limitations

Of all the LD-SSTs performed in an outpatient setting in our hospital between 2003 and 2015, there is a relatively small number of tests where a morning cortisol level prior to the test was known. For this reason it was not possible to make a predictive model for the outcome of the LD-SST, which included morning cortisol as a predictive variable. Such a model would have better identified variables that have a predictive value in addition to morning cortisol itself.

Another limitation is the small number of patients that are diagnosed with primary adrenal insufficiency in this study. One of the consequences is the unexpected result of an abnormal LD-SST being less likely when there is a history of APS-associated autoimmune disease. By extension, the final predictor model could be considered better suited for when central adrenal insufficiency is suspected compared with a suspected primary adrenal insufficiency. However, this study was designed to identify predictors of the outcome of the LD-SST regardless of the incidence of primary and central adrenal insufficiency. In this study we cannot extrapolate the results to patients with suspected primary adrenal insufficiency because of the small number of patients with this diagnosis.

The binary logistic regression model of this study was built with data which were collected retrospectively. More research should be done to verify this model in a prospective setting, including a morning cortisol measurement prior to the LD-SST in all subjects.

CONCLUSION

The number of low-dose synacthen tests performed in an outpatient setting can be safely reduced by altering the conventional cut-off values of screening morning cortisol measurements. We propose an upper cut-off value of 375 nmol/l and a lower cut-off value of 145 nmol/l. A normal outcome is more likely when the main reasons for performing the test are fatigue symptoms or hypotension. An abnormal outcome is more likely when glucocorticosteroids are used. Especially when central adrenal insufficiency is suspected, different routes of administration of glucocorticosteroids should be taken into account.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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ORIGINAL ARTICLE

Screening for renal involvement in ANCA-associated vasculitis: room for improvement?

E. Houben[1], J.W. van der Heijden[2], B. van Dam[1], W.A. Bax[1], A.E. Voskuyl[3], E.L. Penne[1]*

[1]Department of Internal Medicine, Northwest Clinics, Alkmaar, the Netherlands, [2]Department of Nephrology, VU University Medical Centre, Amsterdam, the Netherlands, [3]Department of Rheumatology, Amsterdam Rheumatology and Immunology Centre, VU University Medical Centre, Amsterdam, the Netherlands, *corresponding author: tel.: +31 (0)72-5484444, fax: +31 (0)72-5482165, email: e.l.penne@nwz.nl

ABSTRACT

Background: Renal involvement in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) requires prompt and aggressive immunosuppressive therapy. The aim of this study was to evaluate screening practice for renal involvement in AAV and its potential effect on renal outcomes.

Methods: Between 2005 and 2015, ANCA-positive AAV patients in a teaching hospital in the Netherlands were retrospectively included. Complete screening for renal involvement was defined as: assessment of erythrocyturia, proteinuria and serum creatinine within two weeks of the diagnosis of AAV. Characteristics at presentation and at 12 months were compared between patients with and without complete screening.

Results: A total of 109 AAV patients (63% male) were identified with a mean age of 62 ± 14 years. Complete screening for renal involvement was performed in 90 of the 109 patients (83%). Patients with incomplete screening had a lower serum creatinine (86 ± 53 vs. 190 ± 185 µmol/l, p < 0.001) and were more often diagnosed outside the renal department (100% vs. 78%, p = 0.02). Three patients with incomplete screening had a rise in serum creatinine of ≥ 30% at 12 months. Incomplete screening was not associated with the development of end-stage renal disease. Urine analysis of patients with renal biopsy-proven AAV (n = 31) showed erythrocyturia in 58% after one sample and in 94% after three samples.

Conclusion: Screening for renal involvement in AAV was suboptimal, primarily in patients who presented outside the renal department. A higher sensitivity for erythrocyturia is achieved if urine analysis is repeated. Incomplete screening may lead to renal impairment if renal involvement is not treated appropriately.

KEYWORDS

ANCA-associated vasculitis, end-stage renal disease, renal screening practice

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a life-threatening disease that affects multiple organ systems.[1,2] By the time it is diagnosed, renal involvement is present in 60-80% of patients.[3,4] Renal involvement in AAV progresses rapidly and may lead to the need for renal replacement therapy within days.[5] In AAV patients with kidney damage it is generally recommended to immediately start aggressive immunosuppressive therapy (cyclophosphamide or rituximab in combination with glucocorticoids with or without plasma exchange) in order to prevent progression to end-stage renal disease (ESRD).[6-8]

Deterioration of renal function in AAV is often preceded by urinary abnormalities, such as erythrocyturia and/or proteinuria.[9-12] A recent study in AAV patients with crescentic glomerulonephritis showed that renal outcomes were similar between patients with and without renal impairment at diagnosis.[11] This indicates that baseline renal function alone is a poor marker for renal outcomes in AAV. The benefit of aggressive immunosuppressive therapy in patients with crescentic glomerulonephritis and a preserved renal function has not been addressed in randomised controlled trials so far. Nevertheless, observational data showed better renal outcomes if these patients are treated with cyclophosphamide.[11] It is therefore suggested to treat patients with renal AAV and a preserved renal function with aggressive immunosuppressive

therapy, similar to patients with renal impairment at presentation.[11,13]

Early and complete screening for renal involvement is required in order to immediately start adequate treatment. Recent guidelines recommend screening for renal involvement early in the diagnostic process.[14] So far, the implementation of renal screening and its effects on renal outcome in AAV have not been studied. The aim of the present study is to evaluate whether screening for renal involvement is timely and complete in clinical practice in a teaching hospital in the Netherlands and to determine whether the failure of adequate screening had an impact on renal function after 12 months and the development of ESRD. Furthermore we investigated the diagnostic properties of urine analysis that preceded renal biopsy-proven AAV.

MATERIALS AND METHODS

We performed a retrospective cohort study in the Northwest Clinics, a teaching hospital group in Alkmaar and Den Helder in the Netherlands. The local medical ethics committee approved the study and waived the requirement for informed consent. Patients who were positive for ANCA proteinase-3 (PR3) or myeloperoxidase (MPO) between February 2005 and February 2015 were screened for the clinical diagnosis of AAV, in accordance with Watts algorithm entry criteria for epidemiological studies.[15] All AAV patients who were diagnosed within the Northwest Clinics were included in the study. ANCA serology was assessed by indirect immunofluorescence on neutrophil substrate (NOVA Lite® ANCA, INOVA Diagnostics Inc, San Diego, USA) and, if positive, followed by immunoassays for the detection of antibodies to PR3 and myeloperoxidase MPO (Autostat™ II Anti-PR-3 and Anti-MPO ELISAs, Hycor Biomedical Ltd, UK, from February 2005 until August 2012, and EliA™ PR3^S and EliA™ MPO^S run on a Phadia 250 analyser, Thermo Fisher Scientific, Immunodiagnostics, Sweden from August 2012 until the end of the study period).

Medical records of all enrolled AAV patients were reviewed for patient demographic data, the department diagnosing AAV and the date of diagnosis. Furthermore data on renal outcome, including serum creatinine, estimated glomerular filtration rate (eGFR), using the abbreviated Modification of Diet in Renal Disease (MDRD) equation[16] and the development of ESRD at 12 months after diagnosis were recorded. The Birmingham Vasculitis Activity Score for Wegener's granulomatosis (BVAS/WG)[9] was calculated in all patients based on symptoms at presentation. Renal involvement was defined as either kidney biopsy-proven AAV or renal involvement in accordance with the BVAS/WG. The patient's medical records were reviewed for complete screening for renal involvement within two weeks before or after the diagnosis of AAV. Complete screening for renal involvement was defined in accordance with the Dutch guideline 'Diagnostics of small-vessel vasculitis'[14]: assessment of serum creatinine and assessment of erythrocyturia and assessment of proteinuria. Proteinuria was defined as ≥ 500 mg/24 hours in accordance with proteinuria in the Vasculitis Damage Index.[17] Erythrocyturia was defined as ≥ 10 red blood cells/high power field, in accordance with the BVAS/WG.[9] Renal impairment was defined as serum creatinine ≥ 125 μmol/l, in accordance with BVAS version 3.[18] All samples of serum creatinine and urine analysis three months prior to the biopsy were recorded in patients with renal biopsy-proven AAV.

Statistical analysis

The characteristics of patients who received complete screening for renal involvement within two weeks were compared with characteristics of patients without complete screening. A Wilcoxon signed-rank test was used to analyse the difference between serum creatinine at diagnosis and at 12 months in each group. In addition, renal outcomes defined as the development of ESRD and/or a rise in serum creatinine of > 30% at 12 months were compared between the two groups. The analysis was repeated with complete screening for renal involvement within four weeks instead of two weeks before or after the diagnosis of AAV. Chi-square tests, unpaired Student t-tests and Mann-Whitney's U tests were used where appropriate. A p value < 0.05 was considered statistically significant. For data management and statistical analysis, Statistical Package for Social Sciences (SPSS®) version 20.0 was used.

RESULTS

Between 1 February 2005 and 1 February 2015 a total of 239 patients tested positive for MPO or PR3 ANCA, of which 119 patients (50%) were diagnosed with AAV. The remaining 120 patients were diagnosed with inflammatory bowel disease (n = 24), other rheumatic diseases (n = 23), infection (n = 11), other (n = 29) or unknown (n = 2) diagnosis, or had unclassified symptoms (n = 31). After the exclusion of AAV patients who were diagnosed in a different hospital (n = 10), 109 patients were enrolled in this study. Patient characteristics are summarised in *table 1*. In short, the mean age was 62 ± 14 years and 63% were male. The median time between the first hospital visit with an AAV-related symptom and the diagnosis AAV was six weeks (interquartile range (IQR) 2-44).

Screening practice

In 90 of the 109 patients (83%) screening for renal involvement was completed within two weeks before

Table 1. *Baseline characteristics of 109 AAV patients*

Age (years, mean ± SD)	62 ± 14
Male sex (no, %)	69 (63)
Serum creatinine µmol/l (median, IQR) Serum creatinine < 125 µmol/l (no, %)*	102 (70-207) 66 (61)
Renal involvement (no, %)**	66 (61)
Lung involvement (no, %)**	50 (46)
Ear nose throat involvement (no, %)**	49 (45)
Skin and soft tissue involvement (no, %)**	21 (19)
Arthritis/arthralgia's (no, %)**	42 (38)
BVAS/WG (median, percentiles)	5 (4-7)
MPO ANCA (no, %)	45 (41)
PR3 ANCA (no, %)	64 (59)
Patients with biopsy proven AAV (no, %)***	50 (46)
Weeks between first hospital visit and diagnosis AAV (median, IQR)	6 (2-44)

*Serum creatinine as far as tested at presentation. **Organ involvement defined in accordance with items on the BVAS/WG. ***Biopsy sites were: kidney (n = 31), lung (n = 3), skin (n = 11) and nasal mucosa (n = 5). SD = standard deviation, IQR = interquartile range, BVAS/WG = Birmingham Vasculitis Activity Score for Wegener's granulomatosis, MPO = myeloperoxidase, ANCA = antineutrophil cytoplasmic antibody, PR3 = proteinase-3.

or after the diagnosis. Of the 19 patients (17%) without complete renal screening: assessment of proteinuria was missing in all patients, urine sedimentation for erythrocyturia in 12 patients and serum creatinine in one patient. Screening in these patients was completed within four weeks in four patients, within two months in seven patients and within four years in three patients. In five patients, screening for renal involvement was not completed during a median follow-up of 2.2 years.

In comparison with patients with complete renal screening, patients with incomplete renal screening had a lower serum creatinine (median 70 (56-89) vs. 109 (74-248) µmol/l, p = 0.001) and a lower BVAS/WG (median 4 (3-7) vs. 5 (4-7), p = 0.03) (*table 2*). Notably, median BVAS/WG did not differ significantly after excluding erythrocyturia from the BVAS/WG.

All patients (100%) diagnosed with AAV in the renal department had complete renal screening, as compared with 78% of patients who were diagnosed in other departments (p = 0.02, *table 2* and *table 3*). Of the 88 patients who were diagnosed with AAV in other hospital departments than the renal department, 54 patients (61%) developed renal involvement at any time during follow-up. Repeating the analysis using a cut-off for renal screening of four weeks instead of two weeks before or after the diagnosis yielded similar results.

Most patients with complete renal screening, (n = 72, 80%) were treated with a cyclophosphamide-based regimen

Table 2. *Characteristics of patients who were completely screened for renal involvement and patients who were not completely screened. Complete screening included: assessment of serum creatinine and urinalysis for erythrocyturia and proteinuria within two weeks of the diagnosis of AAV. Other induction regimens than cyclophosphamide in the group with complete screening were: glucocorticoids with/without azathioprine (n = 14), rituximab (n = 1), methotrexate (n = 1), mycophenolate mofetil (n = 1), unknown due to referral to another hospital for induction treatment (n = 1). Other induction regimens in the group without complete screening were: glucocorticoids with/without azathioprine (n = 11) or methotrexate (n = 1)*

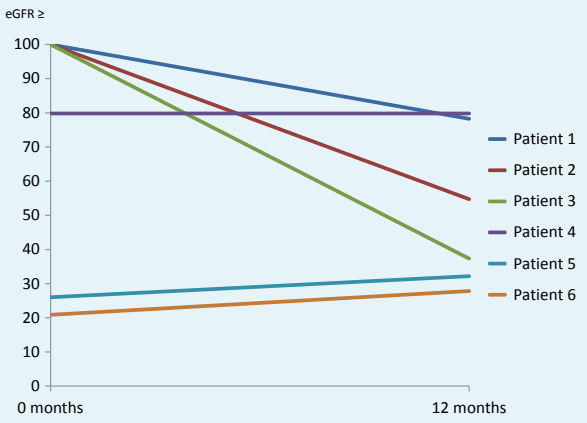
	Complete n = 90	Incomplete n = 19	p-value
Age (mean, SD)	62 ± 13	63 ± 19	0.59
Male sex (no, %)	58 (64)	11 (58)	0.82
Anti-PR3 positivity (no, %)	55 (61)	9 (47)	
Anti-MPO positivity (no, %)	35 (39)	10 (53)	0.27
Serum creatinine µmol/l (median, IQR)	109 (74-248)	70 (56-89)	0.001
Serum creatinine < 125 µmol/l (no, %)	49 (54)	17 (89)	0.01
BVAS/WG (median, IQR)	5 (4-7)	4 (3-7)	0.03
Cyclophosphamide based induction regimen (no, %)	72 (80)	7 (37)	< 0.001
Need for renal replacement therapy at 12 months (no, %)	7 (8)	0 (0)	0.21
Rise in serum creatinine of ≥ 30% at 12 months (no, %)	11 (12)	3 (16)	0.77

SD = standard deviation, IQR = interquartile range, MPO = myeloperoxidase, ANCA = antineutrophil cytoplasmic antibody, PR3 = proteinase-3, BVAS/WG = Birmingham Vasculitis Activity Score for Wegener's granulomatosis.

Table 3. *Complete screening performed within two weeks at different departments*

Department	AAV patients diagnosed (no)	Complete renal screening (no, %)	Renal involvement during follow-up (no, %)
Internal medicine	33	29 (88)	27 (82)
Nephrology	21	21 (100)	20 (95)
Pulmonology	21	14 (67)	9 (43)
Otolaryngology	13	8 (62)	4 (31)
Rheumatology	13	12 (92)	9 (69)
Neurology	3	2 (67)	1 (33)
Cardiology	1	1 (100)	1 (100)
Dermatology	1	0 (0)	0 (0)
Geriatrics	1	1 (100)	1 (100)
Family medicine	1	1 (100)	1 (100)
Gastroenterology	1	1 (100)	1 (100)
Total	109	90 (83)	74 (68)

Figure 1. *Kidney function at diagnosis and after 12 months in 6 patients with incomplete renal screening that developed renal involvement during follow-up. Three patients showed a decline in eGFR. In patient 1: a urinary sediment 9 days after diagnosis and after the initiation of treatment did not show erythrocyturia. However, a urinary sediment 6 weeks prior to the diagnosis did show erythrocyturia. In patient 2: the first urinary sediment was performed one month after diagnosis and showed erythrocyturia and proteinuria. The delay in treatment was 2 months. In patient 3: a urinary sediment 3 days prior to diagnosis showed erythrocyturia. Proteinuria was not assessed. Cyclophosphamide was directly started at diagnosis based on severe pulmonary involvement*



for induction of remission. In patients without complete screening, seven patients (37%) were treated with a cyclophosphamide-based regimen (*table 2*). A total of 79 patients (73%) were treated with azathioprine and glucocorticoids for remission maintenance.

Renal prognosis

The median serum creatinine declined from 109 (74-248) to 103 (82-163) µmol/l in patients with complete screening ($p = 0.20$) and rose from 70 (56-89) to 81 (69-92) µmol/l in patients without complete screening ($p = 0.65$). None of the patients with incomplete renal screening developed ESRD. Of the 19 patients with incomplete screening, renal impairment or urinary abnormalities were documented in six patients at any point during a median follow-up of 5.2 years (2.1-9.7). Three of these patients had a decline in kidney function over the 12 months after diagnosis (*figure 1*). In all three patients the deterioration of kidney function coincided with erythrocyturia. In one patient the deterioration of kidney function coincided with proteinuria. Proteinuria was not assessed in the other two patients. In one patient there was a delay in treatment of two months. In the other two patients treatment was initiated at diagnosis. Of these three patients, one was treated with cyclophosphamide and two were treated with prednisolone induction therapy.

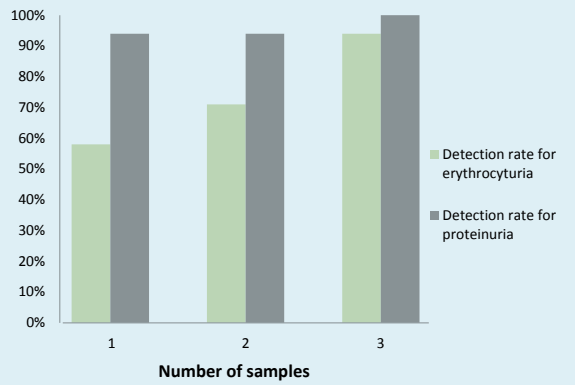
Laboratory findings in patients with kidney biopsy proven AAV

In 35 patients a kidney biopsy was performed, of which 31 were typical for AAV and four were inconclusive. The kidney biopsies were performed as part of the initial diagnostic process. The indication for a biopsy was established based on clinical decision, not on a standardised protocol. Of the 31 patients with kidney biopsy proven AAV, five (16%) did not have renal impairment. A median of three (2-4) urinary sediments were collected and examined for erythrocyturia in the three months preceding the biopsy. Results from these urine analyses were variable within these patients. In 18 of the 31 patients (58%), all urine samples showed erythrocyturia. Three samples were required to detect erythrocyturia in 94% of patients (*figure 2*). In 29 of 31 patients proteinuria was detected in all samples (*figure 2*). The number of required samples for the detection of erythrocyturia or proteinuria was not related to kidney function.

DISCUSSION

In this cohort of AAV patients from a teaching hospital in the Netherlands, screening for renal involvement was performed in 83% of AAV patients within two weeks before or after the diagnosis. Patients with normal kidney function and patients who presented outside the renal

Figure 2. *Detection rate for erythrocyturia and proteinuria in 31 patients with biopsy-proven renal involvement in AAV*



department were at risk of incomplete screening for renal involvement, which may ultimately lead to kidney function loss. In three patients with incomplete screening for renal involvement, kidney function decreased in the year after diagnosis; two of these patients were not treated with appropriate immunosuppressive induction therapy covering renal involvement. Unawareness of renal involvement may have played a role in the choice for the type of immunosuppressive agents in these patients and therefore may have contributed to the kidney function loss. The question arises whether all AAV patients require full renal screening. Although the clinical course of patients with AAV is variable, in most patients the acute phase of systemic vasculitis is preceded by a phase with more mild symptoms.[11,19] During this phase of the disease, many patients suffer from upper respiratory complaints and arthralgia. Patients then usually progress to a more acute phase of the disease, in which rapidly progressive renal failure is a common feature.[5,19] Unfortunately, if renal involvement is diagnosed too late, some patients will have already developed severe kidney damage, occasionally with the need for renal replacement therapy.[5,10] In our cohort 61% of AAV patients who were diagnosed outside the renal department developed renal involvement at any time during follow-up. This indicates the high occurrence of renal involvement in AAV patients who present with other than renal symptoms and emphasises the necessity of complete and repeated renal screening in all patients.

Early screening for renal involvement may have considerable clinical implications. So far randomised controlled studies have not assessed the benefit of aggressive immunosuppressive therapy specifically in patients with early renal disease without loss of renal function. However, observational studies suggest that patients with urinary abnormalities but preserved renal function benefit from aggressive treatment. As already briefly mentioned in the introduction, Hanaoka and colleagues studied 27 patients with biopsy-proven renal involvement, of which 12 patients had preserved eGFR. These patients were divided into two groups according to intravenous cyclophosphamide exposure. At three-year follow-up, patients without cyclophosphamide treatment had significantly lower eGFR than those with cyclophosphamide treatment (42.1 vs. 62.1 ml/min/1.73 m^2, p = 0.01).[11] It is therefore suggested that when patients with renal AAV and urinary abnormalities but a preserved eGFR are treated with aggressive immunosuppressive therapy, irreversible damage due to glomerulonephritis can be prevented.[2,11,13] Apart from the direct therapeutic implications of renal screening, renal baseline parameters also serve the interpretation of future laboratory variables. Current guidelines recommend urine analysis at each patient visit in order to screen for a possible renal relapse or therapy toxicity.[6,20] Knowledge on the course of erythrocyturia (new onset/decreasing) enhances comprehension of disease activity and can guide clinical decision-making.

Based on our findings, we agree with the Dutch guideline 'Diagnostics of small-vessel vasculitis'[14] that screening for renal involvement should include serum creatinine and urine analysis for both erythrocyturia and proteinuria, early in the diagnostic process. In addition, we found that a higher sensitivity for erythrocyturia is achieved if urine sediments are repeated up to three times. Urinary abnormalities in AAV with a preserved renal function require a renal biopsy in order to determine renal involvement. If a renal biopsy confirms renal involvement of AAV, aggressive immunosuppressive agents are indicated. Screening for renal involvement in the diagnostic process of AAV may serve two purposes. First, if erythrocyturia, proteinuria or a rise in serum creatinine are present, this may support the diagnosis of AAV. Second, if AAV is diagnosed based on other findings, screening for renal involvement establishes the extensiveness of the disease and may guide the choice of therapy.[2,8,11] If AAV is suspected in patients outside the internal medicine/nephrology/rheumatology department, early consultation of a physician with expertise in the field of nephrology is suggested.

To our knowledge, this is the first study evaluating the adequacy and reproducibility of screening for renal involvement in AAV patients in clinical practice. Hence, it is unknown to what extent these results would apply to other centres. However, the presence of renal involvement in our population seems consistent with previous reports.[3,4] Furthermore, the number of patients with biopsy proven renal vasculitis (n = 31) in our study was relatively low. However, previous studies found comparable laboratory findings preceding renal biopsy-proven AAV.[21,22] In this study the median BVAS/WG was 5.0 (4-7) (mean 5.8 ± 2.8).

These results were slightly lower than in the Rituximab in ANCA-Associated Vasculitis (RAVE) trial (mean 8.5 ± 3.2) and in the Wegener's Granulomatosis Etanercept Trial (WGET) (mean 6.9 ± 3.4).[23,24] These higher scores could be explained by study selection criteria in the RAVE trial: an indication for cyclophosphamide and BVAS/WG ≥ 3. Furthermore, the slightly higher BVAS/WG in these trials may be due to the prospective collection of data. Although the historical patient files were of high quality, the retrospective design of our study may account for an information bias on documented symptoms and in some cases the exact date of the diagnosis.

In conclusion, in this cohort screening for renal involvement was performed within two weeks of the diagnosis in the majority of AAV patients. However, especially in patients with normal eGFR and a first presentation to other departments than the renal department, there may be room for improvement. These results suggest that a multi-disciplinary collaboration is warranted for an optimal diagnostic process. More awareness for the clinical features of renal involvement in AAV is a key element in the prevention of irreversible kidney damage.

DISCLOSURES

All authors declare no conflicts of interest.

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CASE REPORT

IgG4-related disease: a disease we probably often overlook

I.M. Celis[1]*, R.L. Kriekaart[1], R.P. Aliredjo[2], E.G. van Lochem[3], M.J.D.L. van der Vorst[1], R. Hassing[1]

Departments of [1]Internal Medicine, [2]Pathology and [3]Immunology, Rijnstate Medical Centre, Arnhem, the Netherlands, *corresponding author: tel.: +31 (0)88-0058888, email: imrecelis@hotmail.com

ABSTRACT

IgG4-related disease (IgG4-RD) is an increasingly recognised entity characterised by tumefied lesions that can affect multiple organs. Awareness of IgG4-RD is important, as it has been shown to mimic other diseases and may result in irreversible organ damage if not treated. If suspected, immunostaining for IgG4-positive plasma cells is essential for diagnosis and revision of old biopsies may be necessary.

KEYWORDS

IgG4-related disease (IgG4-RD)

What was known on this topic?
IgG4-RD is a disorder we often fail to recognise because it is considered to be rare and most clinicians are not familiar with its manifestations. Information and treatment regimens were mostly based on information from Japanese case reports, but over the past years, IgG4-RD is increasingly gaining worldwide attention, including in the Netherlands.[4-7]

What do these cases add?
Awareness of IgG4-RD is important as it may mimic other diseases (e.g. infections and malignancies) and it can take years before it is diagnosed. Delay in treatment may result in irreversible organ damage. If suspected, additional immunostaining for IgG4 plasma cells is essential for diagnosis. Revision of previously performed biopsies for specific findings of IgG4-RD may be necessary, as we will demonstrate in this article.

INTRODUCTION

IgG4-related disease (IgG4-RD) is a rare immune-mediated inflammatory disorder that predominantly affects elderly men (over 65 years of age). Calculated incidence rates in Japan are 2.8-10.8 per 1 million people.[1] It is characterised by tumefied lesions that can affect various organs simultaneously or consecutively.
IgG4-RD was not recognised as a systemic condition until the early 2000s when extra pancreatic manifestations were identified in patients with autoimmune pancreatitis type 1.[2] Many medical conditions that have long been viewed as conditions confined to single organs (e.g. Küttner's tumour, Mikulicz's disease, retroperitoneal fibrosis, the fibrosing form of Hashimoto's and Riedel's thyroiditis) are now considered to be part of the spectrum of IgG4-RD. Although IgG4-RD is increasingly gaining international attention, it is still an unrecognised disease, even more so in children. A recently published article provides an overview of all reports published on IgG4-RD in children.[3] We present two patients with IgG4-RD, who had symptoms for many years. Prior investigations, including tissue biopsies, failed to diagnose the disease.

CASE REPORTS

Patient 1
A 72-year-old man was examined because of a renal mass in his right kidney and pulmonary nodules suggestive of malignancy (*figure 1*). Medical history revealed prostate cancer (2012), abdominal aortic aneurysm and retroperitoneal fibrosis (2006) with bilateral hydronephrosis that resulted in functional loss of the right kidney. A nephrostomy catheter was inserted for the left kidney.
In 2014, a PET-CT scan showed several fluorodeoxyglucose (FDG) positive pulmonary nodules and FDG uptake in the thyroid gland for which a diagnostic hemithyroidectomy was performed after cytology remained inconclusive. Histology showed diffuse inflammation. Diagnosis of Hashimoto's thyroiditis was made based on radiological and biochemical characteristics.

The patient complained of fatigue and dyspnoea. Several biopsies of the pulmonary lesions showed chronic inflammation and fibrosis, but no malignancy. Because high suspicion of malignancy remained, a wedge excision of the lung was performed. Histology showed significantly increased plasma cell infiltration and focal storiform fibrosis but no obliterative phlebitis (*figure 2*). Additional immunostaining showed 62/high-power field (HPF) IgG4-positive plasma cells and an IgG4/IgG ratio of 0.42 (*figure 3*). Serum IgG4 was elevated. Based on these results, IgG4-RD was diagnosed.

Revision of previously performed biopsies (with additional IgG4 immunostaining) also showed findings characteristic of IgG4-RD in the retroperitoneum and thyroid (e.g. the IgG4-related form of Hashimoto's thyroiditis), but not in the prostate.[8] The aortic aneurysm was assumed to have been caused by IgG4-related aortitis.

A repeated PET-CT scan showed increased FDG uptake in the pulmonary nodules compared with the PET-CT performed in 2014. The renal mass turned out to be a cyst. Treatment with 60 mg prednisone was initiated for two weeks. The dose was tapered to 45 mg after four weeks. A new PET-CT scan showed decreased FDG uptake in the pulmonary nodules. The serum IgG4 level declined and the dose was further tapered (*table 1*).

The patient remained clinically stable until he unexpectedly died of gastrointestinal bleeding without a clear cause, six months after diagnosis. A link with IgG4-RD or prednisone was not considered likely but could not be excluded because no autopsy was performed.

Patient 2

A 56-year-old man was examined for painless cervical and submandibular lymphadenopathy that had been

Table 1. *Laboratory results of patient 1 and 2*

Features	Patient 1		Patient 2		Reference values
Serum	**Before treatment**	**After 4 weeks treatment**	**Before treatment**	**After 2 weeks treatment**	
ESR	35	NA	17	15	1-20 (mm/h)
Haemoglobin	7.9	8.6	8.4	8.4	8.4-10.8 (m) (mmol/l)
Leukocytes	6.7	11.1	5.9	5.7	4.0-11.0 (x10^9/l)
Eosinophils	NA	NA	0.26	NA	< 0.5 (x10^9/l)
GFR	46	40	76	70	> 90 (ml/min/1.73 m^2)
Creatinine	133	149	90	96	60-110 (µmol/l)
CRP	13	15	1	NA	< 10 (mg/l)
Bilirubin	6	NA	13	NA	< 17 (µmol/l)
ALP	81	NA	86	NA	< 120 (U/l)
GGT	23	NA	15	15	< 55 (U/l)
LD	143	NA	188	169	< 250 (U/l)
Albumin	36	NA	41	40	35-50 (g/l)
ANA	Negative	NA	Negative	NA	
IgE	NA	NA	NA	NA	
IgG	17.80	10.90	17.4	17.8	7.00-16.00 (g/l)
IgG 4	2.14	1.10	12.3	9.0	0.08-1.40 (g/l)
Complement C3	1.66	1.53	NA	NA	0.75-1.40 (g/l)
Complement C4	0.47	0.37	NA	NA	0.10-0.34 (g/l)
Urine					
Protein	0.57 g	0.23 g	None	NA	(g/24h)

ESR = erythrocyte sedimentation rate, GFR = glomerular filtration rate, CRP = C-reactive protein, ALP = alkaline phosphatase, GGT = gamma-glutamyltranspeptidase, LD = lactate dehydrogenase, ANA = antinuclear antibodies, IgG4 = immunoglobulin G4, NA = not applicable.

Figure 1. *Patient 1: Chest X-ray: Pulmonary nodules suggestive of malignancy*

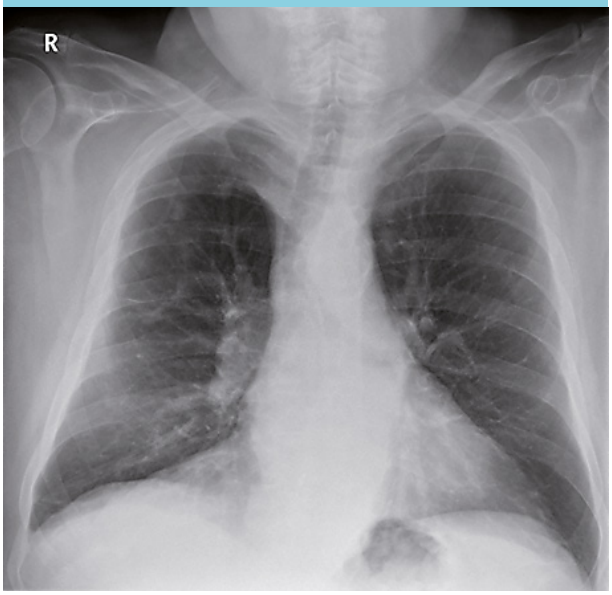


Figure 2. *Patient 1: haematoxylin and eosin staining, slide scanned with Philips digital scanner. This pulmonary nodule shows an area of cellular infiltrate with abundant plasma cells (arrow A) and fibrosis with focal storiform fibrosis (arrow B). The black scale bar in the lower left corner represents 100 µm*

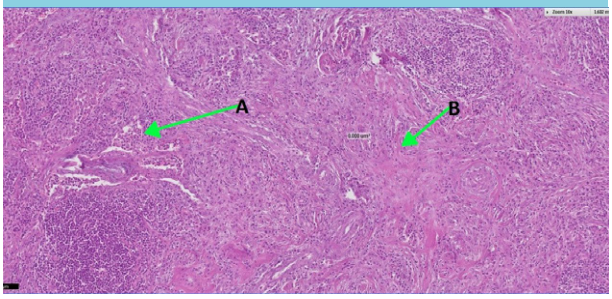
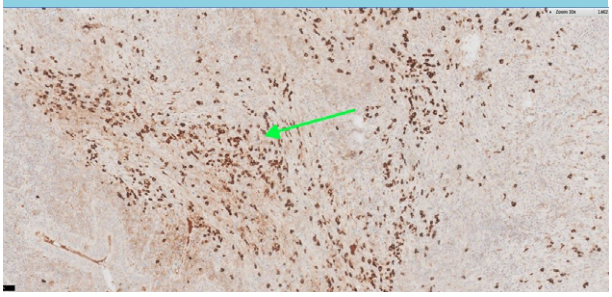


Figure 3. *Patient 1: Immunostaining with antibodies for IgG4 shows clustering of IgG4-positive plasma cells (absolute count of 62/HPF, IgG4/IgG ratio 0.42). The black scale bar in the left lower corner represents 100 µm*



progressive for two weeks. His other complaints were fatigue and generalised new-onset pruritus. He had had chronic cervical lymphadenopathy for several years and earlier investigations failed to diagnose its cause. A lymph node biopsy in 2010 showed lymphoid cells and a starry sky pattern of macrophages. Medical history revealed hypothyroidism and erythema migrans, both of which were treated. A PET-CT scan showed FDG-positive cervical, mediastinal and hilar lymphadenopathy, and two (7 mm) intrapulmonary lesions. There was no FDG uptake in the thyroid. Lymph node biopsy showed a similar pattern as was seen in 2010. Reanalysis for IgG4-RD was requested on the biopsy taken in 2010 and showed 82/HPF IgG4 positive plasma cells and a IgG4/IgG ratio of 0.66 but without fibrosis or phlebitis. Serum IgG level was elevated (*table 1*). Dermal biopsy reported no positive IgG4 plasma cells.

IgG4-RD with lymphadenopathy and possible IgG4-related hypothyroidism and dermatological involvement (though not biopsy proved) was diagnosed. Prednisone 40 mg was started. Evaluation after two weeks showed clinical response with a decrease in lymph node size of 50%. The serum IgG4 level declined and a positive effect on his dermatological symptoms was reported. Prednisone was tapered over months without signs of recurrence during prednisone withdrawal.

DISCUSSION

Here we present two patients in whom IgG4-RD had been present for several years but was not recognised despite prior tissue analyses. Revision of these biopsies for specific features of IgG4-RD proved to be very valuable in the diagnostic process.

Awareness of IgG4-related disease is important as it can affect many organs, although it has certain sites of preference such as the pancreas, orbit, salivary tract and lymph nodes. Clinical symptoms vary according to the spectrum of organs involved. IgG4-RD has been identified to mimic several other diseases such as infections and malignancies and the differential diagnosis is broad.[5,7]

A great diversity of clinical and radiological presentations of pulmonary IgG4-RD has been described and diagnosis can be very difficult.[6,7]

In patient 1 extensive pulmonary analysis excluded malignancy. Features of IgG4-RD were present in the lung and prior biopsies of retroperitoneum and thyroid. In patient 2 mainly lymph nodes were involved, which is a more common presentation of IgG4-RD. Thyroid, pulmonary and skin involvement was suspected but not proven by biopsy.

Both of our patients had elevated serum IgG4 levels at baseline. Though initially viewed as a major diagnostic biomarker, it soon became clear that serum IgG4 lacks adequate sensitivity and specificity for diagnostic purposes when used as a solitary marker.[9,10] However, serum IgG4 levels may be of assistance in the diagnostic process in some cases.[9] Inflammatory markers are not specific for IgG4-RD.

Definite diagnosis of IgG4-RD requires both histopathological information and clinicopathological correlation. Histopathology remains the cornerstone in diagnosis with dense lymphoplasmacytic infiltrates, rich in IgG4-positive plasma cells, storiform fibrosis and obliterative phlebitis as key features. In our both patients the Boston consensus criteria for IgG4-RD were met.[8] A FDG-PET scan (as performed in both patients) is very useful to determine organ involvement and monitor disease activity.[11]

IgG4-RD is thought to be rare, but is probably often overlooked. In both patients it took several years before the diagnosis was made. Prior investigations, including tissue biopsies, failed to diagnose the disease. At that time, the treating clinicians were not aware of the possibility of IgG4-RD and immunostaining for IgG4-positive plasma cells is not a standardly performed procedure in our histopathological analysis.

Attention towards IgG4-RD in pulmonary pathology triggered the pathologist to perform additional immunostaining for IgG4-positive plasma cells when a markedly raised number of plasma cells was seen in the wedge biopsy in patient 1. These results in combination with the patient's symptoms and medical history led to the diagnosis and revision of the previous biopsies. In patient 2 we were more alert to the possibility of IgG4-RD since we had recently diagnosed IgG4-RD in patient 1. We specifically asked for a revision of the biopsy for specific IgG4-RD features, which led to diagnosis.

The pathogenesis of IgG4-RD, and more specifically the role of the IgG4 (auto)antibodies, is still not entirely clear and is the subject of research. In general theory, an antigen-driven immune response drives B cells/Th2 cell to IgG4 production and fibrotic alternations by inflammatory cytokines, such as interleukin (IL)-4, -5, -10, -13 and transforming growth factor (TGF)-β. This inflammation and fibrosis leads to tissue infiltration and swelling.[12]

IgG4-RD often follows a subacute course with vague non-specific symptoms and spontaneous regression may occur. Remission, however, is often temporary and most patients require therapy in order to prevent irreversible organ damage.[13] Once fibrosis is established, therapeutic options are limited. At the time of diagnosis irreversible organ damage was already present in patient 1 (e.g. functional kidney loss due to retroperitoneal fibrosis, aortic aneurysm and hypothyroidism). In both patients treatment was initiated in order to relieve symptoms and prevent future organ damage.

According to the recently published international consensus guidance statement, steroids (initial dose 40-60 mg prednisone) are the first treatment choice and steroid-sparing agents such as azathioprine may be considered as an add-on therapy for patients with a relapse under steroid treatment.[13] Experts are divided on the question whether steroid-sparing agents should be used in combination with glucocorticoids from the start of treatment.[13] Recent articles show promising results of rituximab as a treatment for IgG4-RD.[14,15]

The definite role for steroid-sparing agents and rituximab has to be further established. Recently, good predictors of relapse have been determined in patients treated with rituximab. The higher the baseline values of serum IgG4, IgE, and eosinophils, the greater the risk of relapse and the shorter the time to relapse.[15] Both of our patients responded well to steroids with an improvement in their clinical symptoms, a decrease in IgG4 serum levels and also radiological improvement in patient 1. A PET-CT scan will soon be repeated in patient 2. Patient 1 did not show any signs of a relapse while still on a low dose of steroids at the time he unexpectedly died of gastrointestinal bleeding. Patient 2 remained clinically stable after steroid withdrawal. In case of a relapse, treatment with steroid-sparing agents will be considered.

In conclusion, awareness of IgG4-related disease is important, as it has been shown to mimic other diseases. Delay in treatment may result in irreversible organ damage. We emphasise that, if IgG4-RD is suspected, a specific tissue analysis for IgG4-RD features (with immunostaining for IgG4-positive plasma cells) is requested. In this light, revision of old biopsies may be necessary.

DISCLOSURES

The authors declare no conflicts of interest.

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CASE REPORT

Treatment of cefuroxime-induced neurotoxicity with continuous venovenous haemofiltration

D.G.H.A. van Dam[1]*, D.M.T. Burgers[2], N. Foudraine[1], P.K.C. Janssen[2,3], C. Neef[3,4], J.L.M.L. le Noble[1,4]

Department of [1]Intensive Care, [2]Clinical Pharmacy, VieCuri Medical Centre, the Netherlands, Department of [3]Clinical Pharmacy, [4]Pharmacology and Toxicology, Maastricht University Medical Centre, Maastricht, the Netherlands, *corresponding author: tel.: + 31 (0)77-3205555, fax: + 31 (0)77-3206514, email: dvdam@viecuri.nl

ABSTRACT

A 61-year-old woman with decreased consciousness, myoclonus, tremors, nystagmus and bradypnoea, due to cefuroxime-induced neurotoxicity, was admitted to the intensive care unit. Continuous venovenous haemofiltration (CVVH) rapidly reduced plasma cefuroxime concentrations and improved neurological manifestations within the next few hours. Retrospective pharmacokinetic assessment showed a total cefuroxime clearance of 166 ml/min during the CVVH.

KEYWORDS

Cefuroxime, haemofiltration, intoxication, neurotoxicity, toxicokinetics

What was known on this topic?
Cephalosporin-induced neurotoxicity (CIN) is a rare complication characterised by multiple neurological disturbances ranging from mild encephalopathy to coma. CIN predominantly occurs in elderly patients with compromised renal function and prior neurological disease. In general, CIN can be managed with supportive therapy. However, in case of severe intoxication, renal replacement therapy may be necessary to ensure a rapid decline in serum cefuroxime levels.

What does this add?
This report describes a case of cefuroxime-induced neurotoxicity that was successfully treated with continuous venovenous haemofiltration (CVVH) in an intensive care unit. Furthermore, we performed pharmacokinetic modelling to show that the cefuroxime was effectively cleared due to the CVVH. We obtained a total cefuroxime clearance of 166 ml/min. This case is the first to describe CVVH as a practical, technically feasible and beneficial therapy for CIN.

INTRODUCTION

Cefuroxime is a semi-synthetic second-generation cephalosporin. It has a molecular weight of 446 D, a volume of distribution (V_d) of 9.3-12.8 l, and an elimination half-life ranging between 61.6-80 minutes. It is 33-41% protein bound and predominantly (95%) excreted unchanged in the urine.[1,2]

Cephalosporins, especially cefepime, ceftazidime, and cefuroxime, are associated with neurological disturbances such as mild encephalopathy, status epilepticus, and coma.[3,4] Elderly patients with renal insufficiency and prior neurological disease are prone to the development of cephalosporin-induced neurotoxicity (CIN). Management of CIN comprises cessation of cephalosporin use, initiation of anticonvulsive therapy if indicated, and intermittent haemodialysis in those with compromised renal function.[4]

In general, in haemodynamically unstable ICU patients with oliguric/anuric acute kidney injury, continuous venovenous haemofiltration (CVVH) is the preferred method of renal replacement therapy.[5] Due to its low molecular weight, low protein binding and low V_d, cefuroxime has a high removal rate; therefore, it is expected that serum cefuroxime levels will normalise rapidly to prevent severe neurotoxicity.[6]

We describe a patient with cefuroxime-induced neurotoxicity who was successfully treated with CVVH and regional citrate anticoagulation. Pharmacokinetic

parameters were calculated using MwPharm 3.86 software (MwPharm BV, Zuidhorn, Netherlands).

CASE REPORT

A 61-year-old woman (height 174 cm; weight 80 kg) with a history of chronic obstructive pulmonary disease (Gold IV), type II diabetes mellitus, seronegative rheumatoid arthritis and contracted kidneys was admitted to our hospital. She had suffered a 14-day fever, right flank pain and acute-on-chronic renal insufficiency (serum creatinine 199 µmol/l). She had rose-coloured, cloudy urine.

Abdominal computed tomography scan showed right-sided urolithiasis with urethral obstruction and pelvic dilatation; therefore, a nephrostomy catheter was placed in her right kidney. Intravenous cefuroxime (1500 mg, 3 times daily) and a single dose of gentamicin (400 mg) were administered for suspected urinary tract infection. After four days with clinical improvement, her urine production decreased and the serum creatinine increased (316 µmol/l). Pus (*P. mirabilis*) was observed in the catheter; therefore, two more nephrostomy catheters were placed to drain a suspected pyonephrosis.

Nine days after admission, neurological examination showed a decline in the Glasgow Coma Scale score ($E_3M_5V_4$), horizontal nystagmus, myoclonus and tremors, which necessitated ICU admission. Laboratory examinations showed the following: serum creatinine 440 µmol/l; C-reactive protein, 95 mg/l; leucocyte count, 15.8 $\times 10^9$/l; and serum albumin level, 17 g/l. CIN was suspected and, therefore, cefuroxime was discontinued and CVVH (Prismaflex®) with citrate anticoagulation was started with an AN69ST filter. Blood flow and net ultrafiltration were set at 180 ml/min and 0 ml, respectively. Prismocitrate® and Prismasol® were delivered prefilter and postfilter (2640 and 400 ml/hour, respectively). Plasma cefuroxime concentration at CVVH initiation was 173 mg/l and rapidly declined over the next few hours (*figure 1*). The next day, her general condition improved and all the neurological symptoms resolved completely. Before and after CVVH initiation, total cefuroxime clearance was 11 and 166 ml/min, respectively (*figure 2*), Elimination half-life was 16.8 and 2.6 hours, respectively. V_d of the central compartment was 9.4 l/kg and total V_d was estimated to be 15-20 litres.

Figure 1. *Pharmacokinetic simulation of plasma cefuroxime concentration following intravenous administration of cefuroxime (1500 mg, 3 times daily). Intravenous administration was stopped after nine days and CVVH was initiated. The diamond symbols represent the actual/measured plasma cefuroxime concentrations*

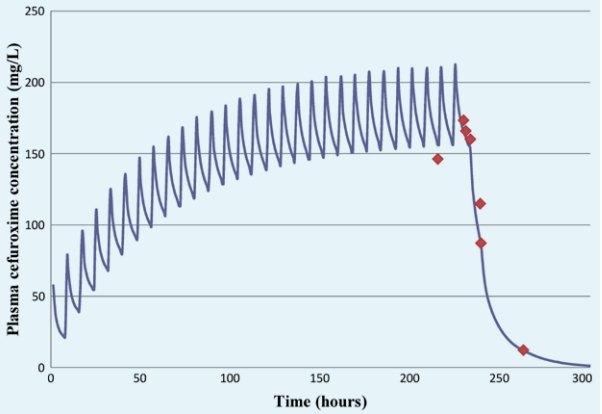
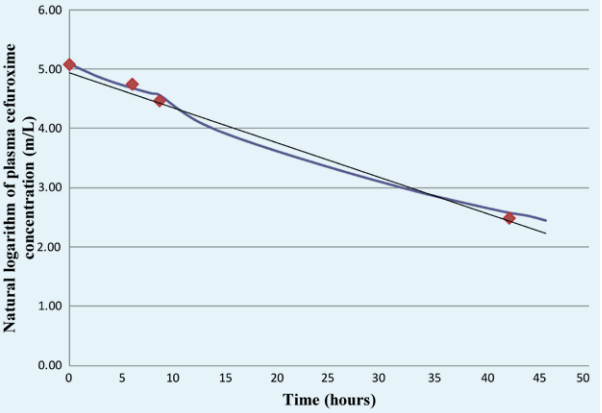


Figure 2. *Natural logarithm of plasma cefuroxime concentration following the initiation of CVVH. The diamond symbols represent the actual/measured plasma cefuroxime concentrations. The natural log transformed plasma cefuroxime concentration was calculated as Lc (C) = -0.059·time (hours) + 4.94 and R^2 was 0.980*



DISCUSSION

We report the case of a critically ill patient with cefuroxime-induced neurotoxicity due to acute-on-chronic renal insufficiency, who was successfully treated with CVVH. CVVH was preferred over intermittent haemodialysis because of haemodynamic instability and practical feasibility. As this type of renal replacement therapy is frequently used in the ICU, it is important to show proof of principle in ICU patients. This is because most published reports describe only intermittent haemodialysis as the rescue therapy for CIN.[7]

The most remarkable finding from toxicokinetic assessments was a rapid decrease in plasma cefuroxime levels to non-toxic levels as a result of the CVVH, which led to a full clinical recovery. We also found that 100% of the 1500-mg single dose of cefuroxime was removed within 2.5

hours following the initiation of CVVH indicating effective cefuroxime removal during neurotoxicity.

There are several possible explanations for the results of the pharmacokinetic assessment. Firstly, the pharmacokinetic characteristics of cefuroxime, including its low molecular weight, hydrophilicity, low V_d and low protein binding, made cefuroxime easily accessible for its clearance during CVVH. Secondly, changes in the protein binding of cefuroxime and thus cefuroxime displacement favours convective clearance during CVVH. The displacement can be caused by acidosis or the levels of bilirubin, uraemic inhibitors, free fatty acids or other displacing drugs in the blood.[6] Thirdly, we observed an increase in total V_d, which is frequently observed in critically ill patients due to capillary leak and oedema. These might have contributed to cefuroxime removal.[8] Because of persistent anuria, clearance by the native kidneys was nil. Furthermore, in a previous study adsorption of cefuroxime by the haemofilter was found insignificant in a similar cohort of patients.[9]

Other possible factors that might have contributed to the total body clearance of cefuroxime during the CVVH were the use of a haemofilter with a larger membrane surface area, a higher blood flow and a higher effluent rate than those used in previous studies. Reports on CIN are uncommon and our finding of an extremely high cefuroxime peak level of 173 mg/l is unique. A previous study reported that, immediately after a 1.0-g bolus injection of cefuroxime was administered to healthy adults, the mean peak plasma concentration of cefuroxime was 99.2 ± 9.6 mg/l. The study also reported that the peak concentrations were not associated with any adverse effects. However, exposure to high concentrations of cefuroxime for a prolonged time might increase the susceptibility to neurotoxicity as was observed in our patient.[10] Dose adjustments are not necessary in a steady state, especially when cefuroxime is administered continuously. It is advised to measure the serum concentration once to be sure that the concentration is in the effective but not in the toxic range. However, changes in renal function may mandate adjustments.[9]

A limitation of the present case is that we did not measure the pre- and post-filter cefuroxime levels; therefore, we could not calculate the sieving coefficient of the haemofilter employed. This also makes it unfeasible to calculate the endogenous and extracorporeal cefuroxime clearances. Finally, we did not correct for protein-bound cefuroxime in plasma.

CONCLUSION

This is the first case to describe CVVH as a practical, technically feasible, safe and effective alternative to acute haemodialysis in cefuroxime-induced neurotoxicity concomitant with anuric renal failure. We showed that the central (vascular) compartment acts as a reservoir of cefuroxime due to the high cefuroxime fraction that is unbound. In addition, the pharmacokinetic analysis was useful in monitoring the concentration and effective clearance of cefuroxime.

DISCLOSURES

The authors declare no conflicts of interest.

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CASE REPORT

Feasibility of long-term continuous subcutaneous magnesium supplementation in a patient with irreversible magnesium wasting due to cisplatin

E.A. Vermeulen[1], M.G. Vervloet[1]* C.H. Lubach[2], S.A.Nurmohamed[1], E.L. Penne[3]

[1]Department of Nephrology and [2]Diabetes Centre, VU University Medical Center Amsterdam, Amsterdam, the Netherlands, [3]Department of Internal Medicine, Northwest Clinics, Alkmaar, the Netherlands, *corresponding author: tel.: +31 (0)20-4441123, e-mail: m.vervloet@vumc.nl

ABSTRACT

A 39-year-old woman presented with severe, uncontrolled and irreversible hypomagnesaemia, following cisplatin treatment in her childhood. Because high-dose oral magnesium supplementation therapy was insufficient and not tolerated, continuous subcutaneous magnesium supplementation was successfully instituted and continued in the outpatient setting. This case demonstrates that continuous subcutaneous magnesium supplementation is effective in maintaining magnesium levels within the normal range, is well tolerated and may provide a long-term solution for chronic hypomagnesaemia due to intractable renal losses.

KEYWORDS

Hypomagnesaemia, magnesium, subcutaneous supplementation, cisplatin

What was known on this topic?

Acute renal toxicity of cisplatin chemotherapy with associated hypomagnesaemia during treatment has been a well-recognised problem. In the treatment of hypomagnesaemia a wide variety of oral magnesium supplements are available, yet all of these are known for their troublesome, mainly gastrointestinal side effects. Magnesium supplementation by intravenous infusions or intramuscular injections are also optional in the clinical setting, although intramuscular injections of magnesium are known to be very painful.

What does this add?

This report presents a case in which cisplatin chemotherapy in childhood caused severe and persisting hypomagnesaemia uncontrollable by oral magnesium supplementation. Continuous subcutaneous supplementation of magnesium proved to be effective in maintaining sufficient levels of magnesium, was well tolerated and induced resolution of several signs and symptoms even after decades. Thereby continuous subcutaneous supplementation can be relevant for all conditions in which magnesium loss is insufficiently controlled by oral magnesium supplementation or high-dose oral magnesium causes intolerable side effects. Moreover, this case is an example of possible irreversible autonomic dysfunction due to chronic and uncontrolled hypomagnesaemia.

INTRODUCTION

Hypomagnesaemia has been reported as a common side effect during and in the period directly following treatment with cisplatin chemotherapy.[1,2] However, severe and persistent tubulopathy causing chronic magnesium wasting many years after cisplatin chemotherapy is rarely seen.[3,4] Hypomagnesaemia has a variety of manifestations, including gastrointestinal symptoms, muscle weakness, muscle cramps, arrhythmia and fatigue. Furthermore, chronic hypomagnesaemia is associated with other electrolyte disturbances, hypertension, atherosclerosis and osteoporosis and it can even cause severe cardiac, neuromuscular and cerebral symptoms.[5,6] Oral supplementation in cases of severe hypomagnesaemia

can be insufficient and can lead to intolerable, mainly gastrointestinal side effects.[7-9] Intravenous administration of magnesium is used in some clinical settings, yet this is not feasible as a long-term solution for chronic and severe hypomagnesaemia.[10] Intramuscular or subcutaneous supplementation of magnesium administration is uncommon in clinical practice and rarely reported, yet these few reports mention its efficacy and tolerability.[11,12] Through this case alternatives for oral or intravenous routes of magnesium administration were explored, in order to achieve long-term adequate levels of magnesium without troublesome side effects.

CASE REPORT

We present a case of a 39-year-old woman with a history of osteosarcoma of the right knee at the age of eleven. Rotationplasty was performed and subsequent cisplatin-based chemotherapy was started. Following treatment she developed symptoms such as cramps mainly affecting the hands, headaches, the feeling of light headedness, altered consciousness and fainting. At the age of 24 low levels of magnesium in her blood were detected (ranging between 0.32 and 0.48 mmol/l), whereas the magnesium levels before treatment with cisplatin were documented to be within the normal range (*table 1*). Subsequently, oral magnesium supplementation was prescribed. Irrespective of the type of oral formulation used (including magnesium gluconate, with relative good bioavailability) this was insufficient to correct the hypomagnesaemia and her clinical symptoms as well as side effects persisted.

In order to study magnesium homeostasis in detail and find an adequate way to administer magnesium that would maintain a sufficient level of serum magnesium and be feasible for the long term, the patient was referred and admitted to our hospital.

Physical examination revealed a healthy appearing young female. Persistent tachycardia at rest (120-130 beats/min) was present and a positive Trousseau sign appeared during blood pressure measurement. Laboratory findings and medication on presentation are shown in *table 1*. Notably, in addition to hypomagnesaemia, hypophosphataemia and hypokalaemia were remarkable. Urine examination confirmed magnesium excretion related to the supplementation dose, demonstrating the inability of the kidney to retain the exogenous magnesium that was supplemented (*figure 1A*). Because of the unusual persisting severity of magnesium losses, additional genetic tests for Gitelman, Bartter 3 and Claudin 16 mutation were performed but revealed no abnormalities. Electrophysiological examinations demonstrated polyneuropathy and autonomic dysfunction. Although extensive neurological assessment was performed, no other explanation for the polyneuropathy and autonomic dysfunction was found apart from the chronic hypomagnesaemia.

To increase reabsorption of magnesium by different mechanisms at several sites of the nephron, low salt diet, acetazolamide and amiloride were consecutively tested, yet all of these interventions were without substantial effect on the magnesium excretion in the urine. Furthermore, magnesium excretion did not respond to hydrochlorothiazide nor did chloride excretion (analysis through a standardised 'thiazide test'), suggesting irreversible damage to the distal tubules as site of magnesium loss.[13,14] Subsequently, continuous high-dose intravenous infusion of magnesium was shown to be effective in increasing magnesium levels to the normal range and was well tolerated, demonstrating a proof of principle that a high dose of supplementation can overcome renal losses. Following this, incremental doses of magnesium sulphate 20% were administrated intramuscularly, subsequently changed to magnesium sulphate 50% to reduce the volume of injections. Although adequate levels of magnesium were achieved through intramuscular administration with additional reduction of some symptoms, the injections were quite painful and caused extensive haematomas. Addition of lidocaine 1% to the magnesium sulphate solution did not reduce pain at the injection site.

Therefore, a trial of continuous subcutaneous magnesium administration was started. Because magnesium is known to be extremely irritative and painful when injected in tissue, a dilution of magnesium together with lidocaine was used. An insulin pump with a subcutaneous needle enabled continuous supplementation of magnesium sulphate 50% combined with lidocaine 2% (2:1 ratio), resulting in a total supplementation of 5 grams of magnesium per 24 hours. With this approach it was possible to achieve an adequate and stable level of magnesium (*figure 1B*, following a combination of adequate intramuscular and intravenous and oral magnesium supplementation). This approach was well tolerated by the patient with acceptable local and no systemic side effects. Therefore, continuous subcutaneous magnesium supplementation was successfully extended towards home practice with a suitable pump system that had to be refilled only once a day, composed of 10 ml magnesium sulphate 50% together with 3 ml lidocaine 2%, running 0.6 ml/hour. Local pain at the insertion site was prevented by mixing a magnesium solution with lidocaine. The location of the subcutaneous needle insertion had to be switched regularly in order to prevent subcutaneous skin lesions and painful congestions.

Magnesium values have been normal ever since, for more than two years of follow-up. Most, but not all symptoms responded well to this therapy. Symptoms such

Table 1. *Laboratory findings before cisplatin treatment, at admission and during continuous subcutaneous magnesium supplementation*

	Pre chemo 1985 (at the age of 11)	Upon admission* (at the age of 39)	During continuous subcutaneous Mg supplementation**	Reference values
Blood results				
Haemoglobin		8.7		7.5-10 mmol/l
Thrombocytes		338		150-400 x 10^9/l
Leucocytes		9.5		4-10 x 10^9/l
Sodium	138	138	142	136-146 mmol/l
Potassium	4.6	3.1	3.2	3.6-4.8 mmol/l
Chloride		102		98-108 mmol/l
Calcium	2.51	2.12	2.35	2.2-2.6 mmol/l
Magnesium	0.79	0.46	0.75	0.7-1.0 mmol/l
Phosphate		0.48	0.66	0.7-1.4 mmol/l
Creatinine	55	59	69	0.49-90 µmol/l
eGFR (MDRD)		> 90	82	> 60 ml/min/1.73m^2
Urine results/24h				
Volume		1800	860	Ml
Sodium		175	134	130-200 mmol
Potassium		85	67	25-125 mmol
Chloride		182		110-250 mmol
Calcium		2.4	4.6	2.5-8.0 mmol
Magnesium		5.6	16.9	3.0-5.0 mmol
Phosphate		14.6	15.7	16-80 mmol
Protein		0.11		< 0.3 g
Creatinine		9.2	8.3	5.3-17.7 mmol

* Medication on admission: magnesium gluconate TID 1000 mg, lisinopril QD 2.5 mg, potassium chloride CR TID 1200 mg, metoprolol QD 12.5 mg, alprazolam QD 0.25 mg PRN, diazepam QD 5 mg CRN, cholecalciferol 50,000 IU once monthly
** Medication: Magnesium sulphate 50% 5000 mg/24 hours SC continuously, lidocaine 2% 60 mg/24 hours SC continuously, potassium chloride CR TID 1200 mg cholecalciferol 50,000 IU once monthly

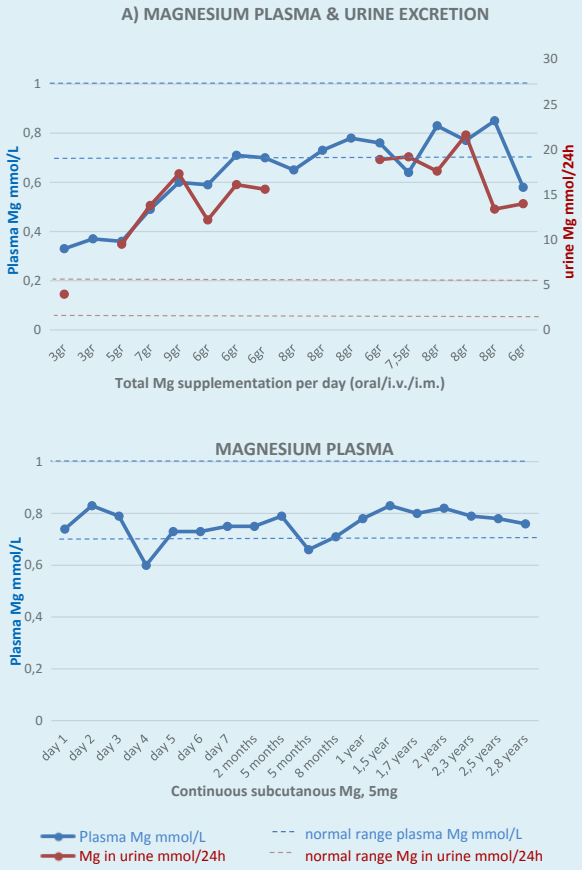
as level of energy, muscle cramps, paraesthesia, hyperventilation, agitation, painful bones and fainting improved remarkably. Yet, some symptoms such as palpitations, light headedness, rigid muscles and insomnia did not show an apparent improvement. Long-term effects of subcutaneous magnesium administration in this case are mild skin lesions at the insertion site, i.e. small and non-painful, indurated areas.

DISCUSSION

Magnesium loss caused by cisplatin chemotherapy treatment is generally transient, probably due to regeneration of the renal epithelium.[15,16] This case is an example of persistent and severe magnesium loss after treatment with cisplatin, which has only rarely been reported.[3]

Oral magnesium supplementation was not sufficiently effective or tolerable and therefore other, parenteral routes of magnesium were explored. Intramuscular injections of magnesium concentrate were effective, yet too painful because of the high concentration to minimise volume load. Continuous subcutaneous magnesium administration proved to be efficacious, maintaining magnesium concentrations in the normal range in the long term with acceptable tolerability. In addition, this case illustrates additional electrolyte disturbances of

Figure 1. *A. Plasma magnesium and urinary excretion during incremental doses of magnesium supplementation (oral/IV/IM). B. Plasma magnesium during subcutaneous magnesium supplementation*



both potassium and renal phosphate loss. Moreover, this case shows that long-term magnesium depletion might induce autonomic dysfunction. Unfortunately, despite long-term normalisation of the magnesium, the symptoms of autonomic dysfunction turned out to be irreversible.

The patient discussed in this case experienced symptomatic hypomagnesaemia, yet the need for magnesium supplementation should be well considered if the hypomagnesaemia is mild or asymptomatic.[17] Robinson et al. reported subjective and objective improvement of magnesium-related symptoms and values, respectively, in patients with chronic hypomagnesaemia due to Gitelman syndrome with the use of slow-release magnesium lactate. Generally, however, serum magnesium concentrations are a poor reflection of total magnesium stores. Moreover, it is unknown if symptoms are the consequence of low magnesium concentration or low total magnesium stores. Based on these considerations it is difficult to provide generally applicable recommendations.

Our case demonstrates the feasibility of continuous subcutaneous magnesium administration as an innovative route of magnesium supplementation due to renal losses. This approach may also be applicable in other medical conditions characterised by magnesium losses, such as Crohn's or Gitelman's disease, where oral supplementation fails.

DISCLOSURES

The authors declare no conflicts of interest.

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PHOTO QUIZ

A man with an unique tongue disorder

S.A.S. van der Bent*, K.B.C. Schamp, J.C. Galvis Martinez

Department of Infectious Diseases, STI Outpatient Clinic, Public Health Service Amsterdam, Amsterdam, the Netherlands, *corresponding author: tel.: +31 (0)20-5555822, fax: +31 (0)20-5555751, email: s.bent@vumc.nl

CASE REPORT

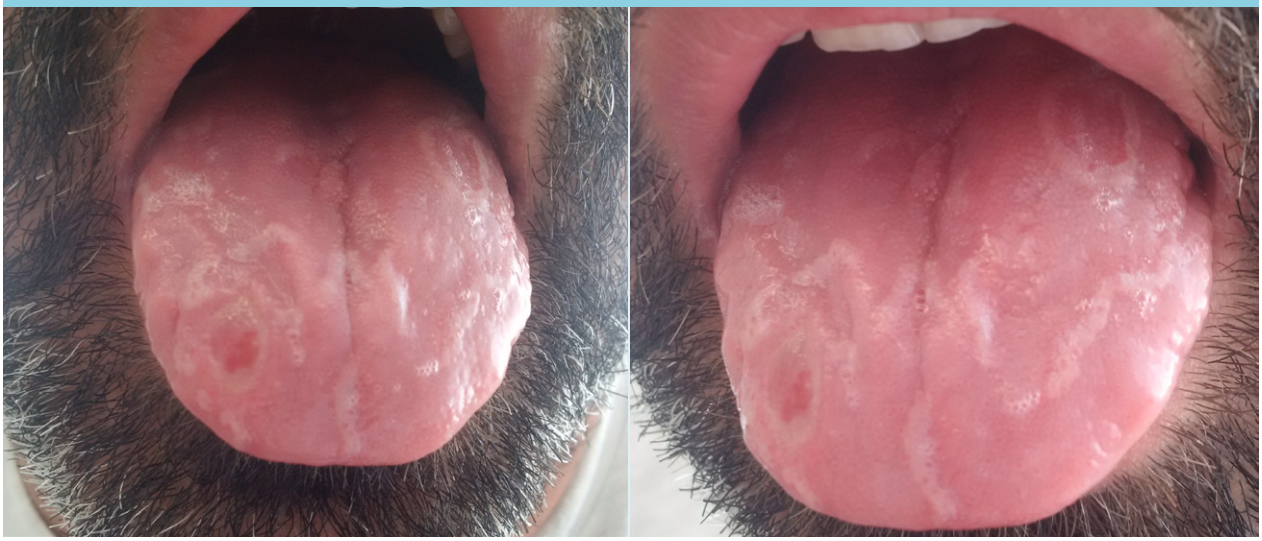
A 39-year-old otherwise healthy HIV-negative man visited the outpatient clinic for sexually transmitted infections (STI) of the local health authority (GGD Amsterdam), because of a three-week history of a painless skin disorder on the tongue. He had no other symptoms and no history of skin rash or ulcerations. In the past few months, he had unprotected insertive and receptive anal and oral sexual intercourse several times.

On physical examination of the upper side of the tongue, we observed multiple sharply demarcated annular and serpiginous greyish white plaques with a symmetric distribution, covering an oval erosion on the distal right side of the tongue (*figure 1*). Photographs were taken with the patient's permission. No other abnormalities were observed on the skin or the oral and anogenital area. There was no cervical lymphadenopathy. His last venereal disease research laboratory (VDRL) test, six months ago, was negative.

WHAT IS YOUR DIAGNOSIS?

See page 40 for the answer to this photo quiz.

Figure 1. *Pictures of the patient showing multiple sharply demarcated annular and serpiginous greyish white plaques with a symmetric distribution, covering an oval erosion on the distal right side of the tongue. Photographs were taken and published with permission of the patient*



ANSWER TO PHOTO QUIZ (PAGE 39)
A MAN WITH AN UNIQUE TONGUE DISORDER

DIAGNOSIS

The differential diagnosis included oral manifestation of syphilis, lichen planus, lingua geographica, stomatitis, candidiasis and herpes simplex. Further research was performed and polymerase chain reaction (PCR) swab for syphilis on the tongue was positive. PCR for herpes simplex virus type I and II, varicella zoster virus and chlamydia were negative. A potassium hydroxide preparation was negative for candida. Blood testing revealed a positive enzyme immunoassay for syphilis and a VDRL titre of 1:8. The HIV test was negative.

On the basis of the clinical and laboratorial findings, the diagnosis of 'mucous patches' was made. Mucous patches, also called plaques muqueuses or snail tracks, is an infrequent manifestation of secondary syphilis.[1]

Syphilis, a sexually transmitted disease, is caused by a spirochete *Treponema pallidum*. Acquired syphilis can be classified into different stages, determined by its activity and infectivity phase. The secondary stage of syphilis results from the systemic spread of *T. pallidum*, occurring weeks or months after the primary infection. Its clinical presentation has a wide variation and includes fever, malaise, headache, sore throat, arthralgias and generalised enlargement of the lymph nodes. Similarly, the cutaneous manifestations vary widely, including a non-pruritic disseminated symmetric maculopapular rash, condylomata lata, corona veneris, lichenoid rash and moth-eaten patchy alopecia.

Oral lesions generally occur in the secondary stage of syphilis, although all stages can exhibit oral disorders. In secondary syphilis, approximately 30% of patients have involvement of the oral cavity. However, oral abnormalities are rarely the solitary manifestation.[2] Mucous patches, although often asymptomatic, are highly contagious. The clinical presentation of mucous patches is annular and oval, slightly raised, greyish white plaques surrounding small superficial ulcerations or erosions. The patches may present in a serpiginous distribution, sometimes termed snail track lesions. They can affect the tongue, buccal mucosa, gingivae, pharynx, larynx, tonsils, epiglottis, aryepiglottic fold and rarely the hard palate.[3] Mucous patches are regarded as the equivalent of the anogenital located condylomata lata, another mucocutaneous manifestation of secondary syphilis.

Syphilis is a treatable disease, but has serious potential complications if not treated. Furthermore, early recognition can prevent further spread of the disease. As STIs are emerging, clinicians should be aware of the different clinical presentations.[4] On suspicion of an STI, oral examination should be performed.

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PHOTO QUIZ

Fever and painful skin lesions after a holiday in Gambia

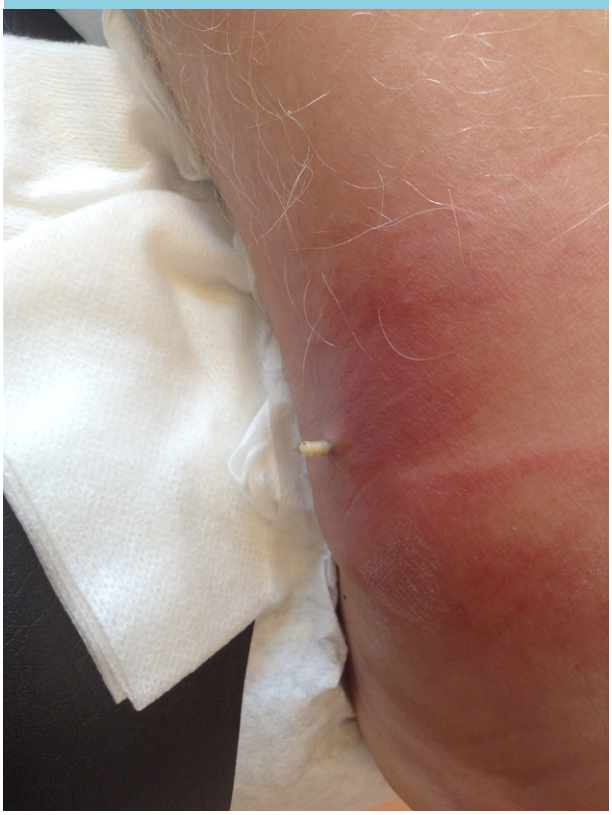
H.R. Bouma[1,2]*, W.D. Kloppenburg[1]

[1]Department of Internal Medicine, Martini Hospital Groningen, Groningen, the Netherlands, [2]Department of Clinical Pharmacy & Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands, *corresponding author: tel.: +31 (0)50-3617870, email: h.r.bouma@umcg.nl

CASE REPORT

A 19-year-old man visited our emergency department because of high fever, headache and painful skin lesions one day after returning from a two-week holiday in Gambia. One week ago, a small itching bug-bite-like lesion appeared on his right lower leg, which gradually increased in size. At presentation to our emergency department, he had an ill appearance and a body temperature of 39.8°C. Two large erythematous lesions with diffuse borders, a central boil-like furuncle and oedema formation were seen on his right lower leg (*figure 1*). The patient had a painful, mobile, weak-elastic, round lump, 2 cm in diameter, in his right groin. Laboratory analysis revealed leukocytosis (15.3 x 10^9/l, of which 13.4 x 10^9/l neutrophils) and an increased C-reactive protein (51 mg/l). The remainder of the examination did not reveal any relevant abnormalities.

Figure 1. *Skin lesion on the lower leg*



WHAT IS YOUR DIAGNOSIS?

See page 42 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 41)

FEVER AND PAINFUL SKIN LESIONS AFTER A HOLIDAY IN GAMBIA

DIAGNOSIS

Based on the clinical image, myiasis with secondary bacterial cellulitis was diagnosed. The larvae were removed by applying gentle pressure to the tissue surrounding the furuncles (*figure 2*) and patient was treated with co-amoxiclav (according to the local protocol for the treatment of cellulitis caused by an unknown causative organism) upon admission to our hospital. He recovered well and was discharged in good condition three days later. Myiasis is an infection due to dipteran larvae (maggots), from *Dermatobia hominis* (human botfly) and *Cochliomyia hominivorax* (New World screwworm) in South America, as well as from *Cordylobia anthropophaga* (tumbu fly) in Africa.[1,2] The disease is mostly seen in travellers returning from South America and sub-Saharan Africa.[1,2] While infection of the skin leads to cutaneous furuncular myiasis or wound myiasis, the larvae can also infect natural body orifices or lead to internal infections (e.g. gastrointestinal, urogenital). Fever is not a classical presenting symptom, but may reflect the presence of a secondary bacterial infection as may arise due to (auto)manipulation. Therapy consists of removal of the larvae, which should preferably be done by occlusion of the opening (e.g. by applying petroleum jelly/vaseline or nail polish). Due to the risk of partial removal of the larvae, manual or surgical extraction should only be performed if occlusive therapy fails.[2,3] Surgical extraction is the initial treatment of choice in cases of ocular involvement and scalp infestations in very young children due to the risk of a potentially fatal cerebral myiasis.[3] Secondary bacterial infection should be prevented by treating the wound locally with an antiseptic and, if there is high suspicion of secondary bacterial infection, treated with antibiotics aimed at the eradication of skin pathogens (e.g. flucloxacillin).[2]

Figure 2. *Extracted larvae*

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PHOTO QUIZ

An old male with multiple hotspots on ^{18}F-FDG PET-CT

L. Bahler[1]*, F. Holleman[1], H.J. Verberne[2]

Departments of [1]Internal Medicine and [2]Nuclear Medicine, Academic Medical Center, Amsterdam, the Netherlands, *corresponding author: tel.: +31 (0)20 5665981, fax: +31 (0)20 6914904, email: l.bahler@amc.uva.nl

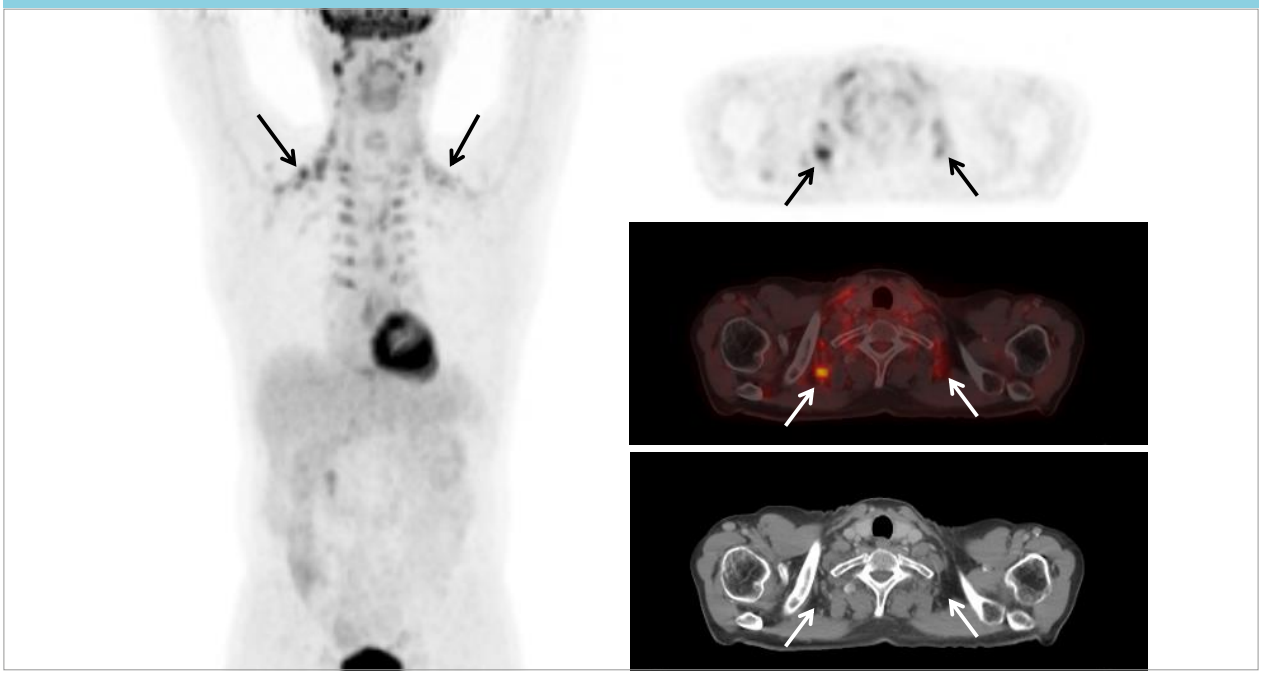
CASE REPORT

A 61-year-old man was referred to our hospital with a four-month history of dysphagia. These complaints were caused by a distal squamous cell carcinoma of the oesophagus. For staging of the oesophageal carcinoma the patient underwent ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) computed tomography (CT), performed one hour after administration of 192 Mbq ^{18}F-FDG with a blood glucose level just prior to administration of 3.9 mmol/l. The ^{18}F-FDG PET-CT revealed increased ^{18}F-FDG uptake in the primary oesophageal carcinoma without evidence of (loco-regional) lymph node or distant metastases. The PET-CT also showed increased ^{18}F-FDG uptake at several other areas (*figure 1*).

WHAT IS YOUR DIAGNOSIS?

See page 44 for the answer to this photo quiz.

Figure 1. *18F-FDG PET-CT of a 61-year old male with multiple hotspots. Left: coronal image of 18F-FDG PET-CT. Right: three transverse images of 18F-FDG PET-CT (from the top down: 18F-FDG PET, combined 18F-FDG PET-CT and CT). Arrows indicate some of the hotspots which are located cranially of the trapezius muscle and at multiple paravertebral locations*



ANSWER TO PHOTO QUIZ (PAGE 43)

AN OLD MALE WITH MULTIPLE HOTSPOTS ON ^{18}F-FDG PET-CT

DIAGNOSIS

The high ^{18}F-FDG uptake is located in adipose tissue cranial of the trapezius muscle and at multiple paravertebral adipose locations, most likely reflecting metabolically active brown adipose tissue (BAT) (*figure 1*).
Metabolically active BAT is a relatively common finding on diagnostic ^{18}F-FDG PET-CTs with a prevalence of 2-9%.[1] In newborns and children, BAT functions to maintain a stable core temperature by converting calories into heat, when surrounding temperatures drop. In general, the prevalence of active BAT on diagnostic ^{18}F-FDG PET-CTs significantly decreases with increasing age, body mass index (BMI) and/or outdoor temperatures.[1]
In prospective BAT research, where BAT is activated using cold exposure before the ^{18}F-FDG PET-CT, the prevalence of detectable BAT in elderly patients aged over 60 is very low.[2] Furthermore, on diagnostic ^{18}F-FDG PET-CTs, active BAT is more frequently seen in women than in men.[1] Indeed, in cell cultures, testosterone has been shown to inhibit the thermogenic response of BAT.[3] Accordingly, the chance of detecting active BAT in a male patient aged over 60 on a diagnostic ^{18}F-FDG PET-CT is close to zero.
The reason for activation of BAT in this relatively old male might be that the patient was affected by active cancer. The cancer cells might secrete factors that upregulate the expression of genes involved in thermogenesis, leading to activation and/or recruitment of BAT. These mechanisms are closely related to the wasting processes observed in cancer-associated cachexia.[4] At the moment of the ^{18}F-FDG PET-CT scan, the patient had lost approximately 3.5 kg in the past four months and had a BMI of 21.1 kg/m^2.
Furthermore, the scan was performed in January. The outdoor temperatures during that day (mean temperature of 7.9 °C with a minimum of 5.8 °C and a maximum of 10.3°C) but also during the month were low (mean temperature 4.0 °C with a minimum of 1.5 °C and a maximum of 6.41 °C) obtained from sourcing data from the Royal Netherlands Meteorological Institute (KNMI, https://www.weerstatistieken.nl). The low outdoor temperatures might have also contributed to the finding of active BAT.
Although the finding of metabolically active BAT in an old male is rare, it underlines the potential of BAT to regenerate/reactivate in an old male. This finding is important since obesity is apparent in all age categories, including the elderly. Therefore, BAT might be recruited/reactivated in elderly people and thereby function as a target in the treatment of obesity, also in the elderly.
On the other hand, this case underlines the importance of adequate preparation of patients undergoing ^{18}F-FDG PET-CT scans. Active BAT can hamper the interpretation of diagnostic scans especially leading to false-positive negative findings. BAT activity can easily be downregulated by increasing room temperature in preparation of the scan. However, in some cases this is not enough to decrease BAT activity. In cases of persistent BAT activity, administering β-blockers prior to the scan may be helpful since β-blockers have been shown to be very effective in blocking BAT activity. The patient was treated with neoadjuvant chemoradiation and eventually died of complications following the subsequent transthoracic oesophagus-cardiac resection.

DISCLOSURES

The authors declare no conflicts of interest.

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PHOTO QUIZ

A 34-year-old man with back pain

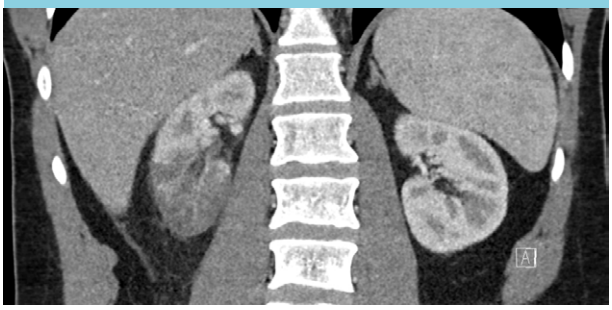
D.J.L. van Twist[1]*, R.J.J.M. van de Laar[1], R.J.B. Brans[2], J.W.J. Refos[3], A.A. Kroon[1]

Departments of [1]Internal Medicine,[2] Radiology, [3]Urology, Maastricht University Medical Centre (MUMC+), Maastricht, the Netherlands, *corresponding author: tel.: +31 (0)43-3877005; fax: +31 (0)43-3875006, email: daan.van.twist@mumc.nl

CASE REPORT

A 34-year-old man with an unremarkable medical history (except for surgical repair of an inguinal hernia several years ago) was referred to the emergency department because of sudden, severe, colicky pain in his back and right flank. Intramuscular injection with diclofenac 75 mg by his general practitioner had no effect on his symptoms. He used no medication, denied traumatic injury, and had no gastrointestinal complaints. At physical examination his blood pressure was 135/85 mmHg, pulse 80 beats per minute, and temperature 36.2° Celsius. Deep palpation of the abdomen, flank, and back was not painful. Laboratory tests revealed slightly elevated inflammatory parameters (i.e., C-reactive protein 49 mg/l, leukocyte count 11.4 x 10^9/l) and an elevated lactate dehydrogenase level of 783 U/l. Urine analysis showed microscopic haematuria (> 200 erythrocytes/µl). The patient was admitted to the urology ward under suspicion of urolithiasis. An abdominal ultrasound and abdominal X-ray, however, showed no abnormalities of the kidneys or urinary tract. Therefore, a computed tomography (CT) scan was performed (*figure 1*).

Figure 1. *Contrast-enhanced CT scan of the abdomen in the coronal imaging plane*



WHAT IS YOUR DIAGNOSIS?

See page 46 for the answer to this photo quiz.

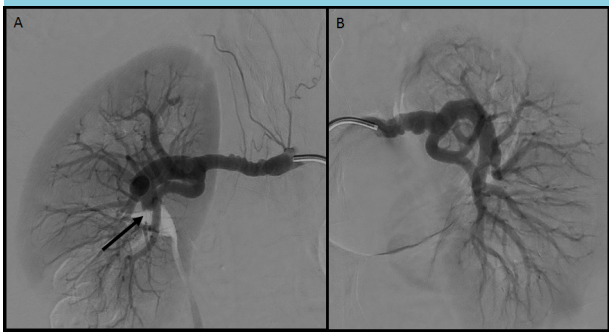
ANSWER TO PHOTO QUIZ (PAGE 45)

A 34-YEAR-OLD MAN WITH BACK PAIN

DIAGNOSIS

The CT scan revealed an infarction of the lower pole of the right kidney as the cause of the acute back and flank pain. There were no signs for urolithiasis. Renal infarction can be the result of a thromboembolism,[1] but echocardiography and CT scan of the aorta did not show any embolic source. In addition, hypercoagulability tests (including anticardiolipin antibodies and lupus anticoagulant) were normal and we found no other clues for vasculitis. As we suspected a renovascular cause we performed diagnostic digital subtraction angiography of the renal arteries (*figure 2*). This shows multifocal fibromuscular dysplasia (FMD) of both renal arteries and occlusion of one of the intrarenal branches of the right renal artery. FMD is a non-atherosclerotic, non-inflammatory vascular disease and a common cause of renovascular hypertension.[2] It is a common misconception that FMD exclusively occurs in young, tobacco-smoking women, which is (as this case underscores) certainly not the case. Although renal infarction is a rare complication of FMD, FMD should be considered if alternative causes for infarction are lacking. Although embolisation of intravascular thrombi from aneurysmal segments has been suggested as the proposed mechanism in FMD-related renal infarction,[3] it is more likely that spontaneous dissection (a common complication of FMD)[4] is the cause in this case. The dilated intrarenal vessel on the angiogram is presumably the false lumen of the dissected artery, which compresses the true lumen, resulting in occlusion of its arterial branches. In this case we decided to refrain from endovascular treatment as the patient was already free from pain at the moment of angiography and there were no signs of hypertension or renal insufficiency, the two indications for intravascular treatment. Therefore, endovascular treatment would not provide any benefit, while the risk for procedure-related dissection is considerable.

Figure 2. *Selective digital subtraction angiography of the right (panel A) and left (panel B) kidney showing multifocal fibromuscular dysplasia (with a typical string-of-beads pattern of the proximal renal artery) of both renal arteries and an acute occlusion of one the intrarenal branches in the right kidney (arrow, panel A)*



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