Glomerulonephritis in mixed cryoglobulinaemia: what treatment?

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Introduction

Mixed cryoglobulinaemia (MC) is a rare systemic disease characterized by circulating cold precipitable mixed immunoglobulins composed of monoclonal IgM rheumatoid factor and polyclonal IgG. Purpura, weakness, arthralgias and glomerulonephritis are the principal clinical manifestations. Rarely gastrointestinal, cardiopulmonary and neurological vasculitis may also occur. Liver disease is frequent. Some patients may remain asymptomatic for years but in many cases the liver disease is progressive and this is a frequent cause of death. MC was called essential until recently because no aetiological factor could be identified. In 1990, however, Pascual et al. [1] reported an association between MC and hepatitis C virus (HCV) infection. Since then it has been recognized that the majority of patients with MC had anti-HCV antibodies and a critical aetiological role has been attributed to HCV infection.

Cryoglobulaemic nephritis

Kidney involvement is frequent in MC, but in many cases renal disease is recognized only years or decades after HCV infection. In a few patients, however, renal and extrarenal signs and symptoms are present at the onset of the disease. The clinical presentation of renal disease may be variable. A number of patients show proteinuria, microscopic haematuria and/or arterial hypertension. Moderate renal insufficiency is frequent. In another 20% of cases renal involvement is heralded by a nephrotic syndrome. In some 20–30% of patients the first renal manifestation is an acute nephritic syndrome with microscopic or macroscopic haematuria, proteinuria and a rapidly progressive deterioration in renal function. A diffuse proliferative and exudative glomerulonephritis resembling a membranoproliferative glomerulonephritis is the most common histological pattern observed. Intraluminal thrombi, glomerular infiltration of monocytes, double-contour appearance of the glomerular basement membrane and renal vasculitis of small and medium-size vessels are frequent. In less severe cases, a mesangial lesion may be seen [2].

Treatment of MC nephritis

Good blood-pressure control is of paramount importance in patients with MC nephritis. Arterial hypertension is common and often severe in MC patients. As in any type of renal disease, hypertension contributes to progression and to cardiovascular disease. The latter represents the main cause of death among patients with MC [3]. Therefore, every effort should be made to maintain blood pressure within the range of recommended values. A combination of antihypertensive agents is usually necessary to achieve this goal.

Because of the frequent association of MC with HCV infection, treatment with the antiviral agent α-interferon (αIFN) is one therapeutic option which has been recommended in MC patients. In two randomized trials [4,5], doses ranging between 1.5 × 10⁶ and 3 × 10⁶ Units were administered three times a week for 23–52 weeks. HCV RNA turned negative in about half of the 42 patients (53%). Most patients had only mild renal involvement and only a few had moderate renal insufficiency. Improvement of systemic signs and serological markers of disease activity such as S-creatinine or circulating cryoglobulins, usually occurred within the first month. Unfortunately, all the patients who responded had a relapse of the disease upon discontinuation of αIFN. More recently a few case reports have shown longer remission when higher doses of αIFN, up to 10 × 10⁶ Units three times a week, were given for a short period [6–9]. Anecdotal observations of reversal of membranoproliferative glomerulonephritis after αIFN have also been reported [10]. From the available information it seems, however, that the benefit of αIFN is transient and is confined to a few patients with mild and/or quiescent renal disease.

It remains unproven whether αIFN plays a favourable role at all in patients with flares of renal activity or with renal insufficiency. From a theoretical point of view, αIFN may even be contraindicated in patients with active renal disease, as its immunostimulating activity might aggravate renal disease and vasculitic lesions [11]. Furthermore, αIFN has myelosuppressive...
effects, probably as a result of its antiproliferative action on haematopoietic progenitor cells. This effect may be enhanced by the concomitant use of ACE inhibitors as reported by Casato et al. [12]. Thus, caution is required when αIFN therapy is adopted. Patients should be monitored carefully and the drug should be stopped if any sign of renal or extrarenal exacerbation of MC occurs.

A different therapeutic strategy aims at introducing measures that interfere with the immune mechanisms responsible for renal damage, e.g. corticosteroids, cyclophosphamide and/or plasmapheresis. A few years ago we reviewed the available literature and compared the results of supportive therapy with those of prolonged treatments with oral corticosteroids, given alone or in association with cytotoxic drugs. Although the results came from retrospective studies and should therefore be interpreted with caution, we were impressed by the fact that the risk of renal death (36 vs 37%), the probability of reversal of renal function (45 vs 48%) and that of maintaining a stable plasma creatinine (18 vs 15%) were similar [13]. No information on the course of untreated patients is available.

Prolonged plasma-exchange plus small doses of prednisone were used with some success in a small number of patients with acute exacerbation of MC nephritis and/or cutaneous vasculitis. However, chronic plasma-exchange treatment must still be regarded as an unproven procedure. Based on the above results prolonged immunosuppression does not appear to be justified in patients with MC nephritis.

Since 1977 we have followed a different therapeutic strategy. We aggressively treat the flares of the disease presenting as nephritic syndrome with renal function impairment, nephrotic syndrome and/or severe cutaneous or visceral vasculitis, by administering intravenous high-dose methylprednisolone (MP) pulses (0.5–1 g each) for three consecutive days. This is followed by 0.5 mg/kg/day of oral prednisone slowly tapering to a maintenance dose of 0.1–0.2 mg/kg/day until MP is withdrawn after 3–6 months. In the most severe cases, patients are also given oral cyclophosphamide 1–2 mg/kg/day for 2 months. Intravenous MP pulses had a dramatic effect on extra-renal manifestations. Fever remitted within a few hours, arthralgias, abdominal pain and leg ulcers promptly improved, while purpura reverted at a slower pace. During 27 episodes of renal exacerbation treated with intravenous MP pulses, plasma creatinine tended to decrease within 1 week in 85% of cases while proteinuria and cryocrit levels decreased more slowly [12]. Although the observation is not controlled and we cannot exclude that some patients improved spontaneously, the fact that in most patients plasma creatinine improved within 1 week after MP pulses seems to be a strong argument in favour of the effectiveness of this treatment. MP pulse treatment can also be used in outpatients, is economic and is relatively safe. Consequently, we feel that, at the moment, MP pulse therapy is the golden standard for the first line treatment of flares of MC.

Conclusions

MC usually begins as a pauci-symptomatic disease which can be aggravated dramatically by involvement of the kidney. The pathogenesis of the disease must be viewed from a different angle after evidence has become available that MC is the result of HCV infection. Although fully satisfactory treatment is not yet available we suggest the following approach in patients with renal involvement. (i) Strict control of hypertension. (ii) Use of αIFN in patients with a low-grade kidney involvement, fully aware of the fact that the doses and duration of treatment have not yet been standardized. Only 50% of patients with MC respond and relapses after αIFN discontinuation are frequent. In preliminary studies in patients with chronic hepatitis C, the combination αIFN and ribavirin, resulted in a higher rate of long-term response than IFN alone. In our opinion this promising approach should also be tried in MC patients. (iii) Long-term treatment with corticosteroids and cytotoxic agents should be avoiding as it does not protect against renal and extra-renal flares, while exposing the patient to the risks of infections, hypertension, cardiovascular disease and neoplasia. (iv) Acute nephritic and vasculitic flare-ups should be treated with high-dose intravenous steroid pulses followed by a short-term course of oral prednisone and cytotoxic drugs.

References


The relative roles of circulating and tissue renin–angiotensin systems

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Introduction

On the one hand the renin–angiotensin system is an endocrine system regulating the level of arterial pressure by influencing arterial resistances and sodium excretion. On the other hand, it is an autocrine–paracrine system participating in tissue remodelling, mainly in the heart, the kidneys, and the vessels. This dual function is based on compartmentalization of the renin–angiotensin system in two sectors, the plasma and the interstitial fluid. Plasma angiotensin II (Ang II) depends almost exclusively on renin secretion for two reasons: (i) the $K_m$ of converting enzyme which transforms angiotensin I (Ang I) into Ang II is much higher than the circulating levels of Ang I, and (ii) in the plasma there is normally an excess of angiotensinogen, the substrate of renin. This explains why plasma Ang II is strictly related to plasma renin, so that the plasma renin assay can be used as a substitute for a plasma Ang II assay. In contrast, the synthesis of Ang II in tissues depends on the local level of converting enzyme. Furthermore the effects of Ang II in the tissues are modulated by the specificities of the target cells and the density of Ang II receptors at the cell surface.

The purpose of this editorial review is to discuss the main experimental data documenting the compartmentalization of the renin–angiotensin system, supporting the idea of distinctive roles of the plasma and the tissue systems. Four questions will be addressed: (i) where is active renin formed and where does the renin–angiotensinogen reaction take place? (ii) where is Ang II formed and how is synthesis of Ang II regulated? (iii) what are the effects of plasma Ang II on its endothelial receptors? (iv) what are the long-term effects of interstitial Ang II on vascular remodelling?

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could not be accounted for by diffusion of these peptides from the plasma, so that by necessity they had to be locally produced [9]. This notion was confirmed by the fact that in heart tissue the levels of Ang II were higher than in plasma [10]. It is thus likely that circulating renin is taken up by the tissues. This had been proposed 15 years ago by Loudon et al. [11]. More recently, Okamura et al. [12] identified immunoreactive renin in the endothelium of human arteries, suggesting a role for the endothelial cells in the uptake of renin and the formation of Ang I. Specific renin receptors have been postulated [13], but the molecular mechanism of renin uptake is still unknown. The issue of how angiotensinogen reaches the interstitial space has also not been resolved. Angiotensinogen in the vessel wall could be synthesized locally [14] or could be taken up from the circulation. The latter process must predominate, since the liver produces almost one-thousand times more angiotensinogen than do peripheral tissues.

**Sites and control of Ang II formation**

Renin secretion is the first regulated step and conversion of Ang I into Ang II by converting enzyme is the second one. This represents local regulation in contrast to the secretion of plasma renin which is an endocrine process. Such local regulation does not influence the level of blood pressure, at least acutely, but is mainly implicated in vascular remodelling. It is essentially dependent of the local expression of converting enzyme.

High concentrations of ACE are constitutively expressed at the luminal surface of vascular endothelial cells and angiotensin-converting enzyme is shed into plasma; therefore it is not a limiting factor for the production of Ang II in the systemic circulation. As demonstrated by Danser et al. [9], the greatest fraction of Ang II is formed in the tissues in which the converting enzyme is the result of inducible expression by non-endothelial cells, e.g. smooth-muscle cells, fibroblasts, and inflammatory cells. Its induction is associated with activation of these cells, for example migration of the smooth muscle cells into the vessel intima, transformation of fibroblasts into myofibroblasts and of monocytes into macrophages. This has led to the proposal that under pathological conditions converting enzyme expression is stimulated. For example, in rats treated with L-NAME, a NO-synthase inhibitor, vascular and myocardial remodelling was associated with increased converting enzyme activity and increased immunodetectable converting enzyme protein in the tissues [15]. Similarly, in experimental cardiac failure induced by coronary-artery ligation, converting enzyme expression was simultaneously diminished in the endothelial cells and increased in the infarcted areas containing activated fibroblasts and inflammatory cells [16]. The hypothesis has been proposed that the level of converting-enzyme induction and the intensity of local lesions, e.g. neointimal formation, were dependent of the converting-enzyme genotype. For example, two strains of rats, differing by the degree of expression of converting enzyme, responded differently to balloon injury of the carotid artery: the vascular lesions were more marked in rats with higher expression of converting enzyme [17]. These experiments are in accordance with studies demonstrating an increased frequency of vascular accidents in patients with the DD genotype which is associated with higher levels of converting enzyme [18].

The density and the cell specificity of Ang II receptors also play a role in vascular remodelling. These receptors are present on fibroblasts, inflammatory cells and smooth-muscle cells. The degree of their expression is regulated by many factors and depends also on the genetic background.

**Effects of circulating Ang II on endothelial cells**

The fraction of Ang II that is generated in the plasma (i) interacts with specific endothelial receptors or (ii) is filtered through the glomerular capillaries and degraded by the peptidases present on the brush border of the proximal tubule epithelial cells. Endothelial cells also participate in the degradation of Ang II by the many peptidases they express including aminopeptidases A and N, and neutral endopeptidase. Several studies demonstrated the presence of type I (AT₁) and type II (AT₂) receptors on cultured endothelial cells. AT₁ receptors are found in murine and human aortic endothelial cells [19]. Endothelial AT₂ receptors have been detected less consistently. Some of the different results may be explained by differences in the status of the cells (quiescent or proliferating) and in their origin (endothelium of large vessels or capillaries) [20]. In vivo expression of AT₁ receptors on the endothelium of isolated rat arteries has also been demonstrated by pharmacological techniques [21]. Endothelial AT₁ receptors exhibit characteristics similar to those of their smooth-muscle-cell counterpart, in particular affinity in the nanomolar range and signal transfer mechanisms including phospholipase C and A₂ activation followed by inositol triphosphate formation and cytosolic calcium mobilization [19]. The biological effects mediated by the AT₁ receptors are both immediate and delayed. The main acute effects are the stimulation of the constitutive calcium-dependent NO synthase activity with production of NO and the release of arachidonic acid providing the substrate for prostacyclin synthesis. NO and prostacyclin mediate the endothelium-dependent vasodilatation of the adjacent vascular smooth muscle cells [21]. This represents a mechanism by which Ang II limits its own vasconstrictor effects. More recently, long-term effects of Ang II on endothelial cells have been described. Ang II upregulates NO synthase expression and via the tyrosine phosphorylation of target proteins, Ang II upregulates expression of several genes implicated in extracellular matrix formation such as type I inhibitor of plasminogen activator (PAI-1), endothelin-1, and metalloproteinases [22]. Ang II is also implicated in the oxidant stress via stimulation of NADPH oxidase with production of superoxide anion [23], which is respons-
ible for the increased adhesion of monocytes to endo-
thelial cells. A possible explanation could be the
induction of the genes of proinflammatory proteins via
the reactive oxygen species-dependent transactivation
of the nuclear factor NFκB. Angiogenesis is another
long-term endothelial effect of Ang II, as shown by
the induction of neovascularization in the rabbit cornea
and in sponge implant in mice after treatment by this
hormone [24].

Long-term effects of locally formed Ang II on
vascular remodelling

Many studies have shown that Ang II exerts long-term
 trophic effects on the vessel wall via activation of the
 AT1 receptors. The main role of Ang II is to increase
protein synthesis leading to cell hypertrophy. This
increase also concerns the contractile proteins. Vascular
remodelling also involves accumulation of extracellular
matrix leading to an increase of collagen, fibronectin
and proteoglycans [25,26]. This effect can be demon-
strated in vitro, thus illustrating that it does not depend
on haemodynamic changes. The effect of Ang II on
the synthesis of the extracellular matrix proteins is for
the most part dependent on an increase in the expres-
sion of transforming growth factor (TGF)-β [26] and
of endothelin [27]. In vivo, treatment with AT1 antag-
onists decreases neo-intimal thickness and diminishes
the collagen content of the vessel wall. It is difficult,
under in vivo conditions, to distinguish between direct
trophic effects of Ang II and the effects of blood-
pressure changes leading to decreased mechanical
strain. The latter represents another signal acting via
adhesion molecules and the cytoskeleton to affect the
biosynthetic properties of the smooth muscle cells. Ang
II also promotes cell growth as demonstrated by the
decrease in myointimal proliferation after treatment
by a converting enzyme inhibitor of rats with vascular
injury [28]. This role of Ang II is mediated by increased
expression of growth factors including platelet-derived
growth factor (PDGF) and basic fibroblast growth
factor (bFGF). Ang II also stimulates the expression
of growth factor receptors.

An essential pathogenic effect of Ang II on the
vessell wall is to increase the oxidant stress. Several
studies by the Atlanta group have shown that NADPH
oxidase activity of the smooth-muscle cells was activ-
ated by Ang II both in vitro and in vivo. This effect
involves an increase in the expression and activity of
p22 phox, which is the membrane subunit of the
enzyme [29]. Increased oxidant stress elicits a trophic
response of smooth-muscle cells to Ang II via two
mechanisms: (i) activation of the transcription factor
NFκB which controls the expression of chemoattrac-
tants, and (ii) transformation of NO into peroxyni-
trites, which are important factors of peroxidation.

Since the AT1-mediated Ang II effects are often
opposed to those depending on AT2 activation, the
role of AT2 receptors in the trophic effects of Ang II
has also been examined but, contradictory conclusions
were obtained. For example, Nakajima et al. [30]
reported that intimal hypertrophy was diminished by
70% after transfection of the AT2 gene, whereas Levy
et al. [31] showed that a 3-week treatment with PD
123519, and AT2 antagonist, had no effect on blood
pressure in rats chronically infused with Ang II, but
nevertheless produced a decrease in aorta hypertrophy
and in the size and the number of smooth-muscle cells
in the aorta media.

Conclusions

The essential messages are (i) Ang II exerts different
effects depending on the cell type with which it first
interacts. The largest fraction of Ang II is formed in
the interstitial fluids and causes contraction of the
smooth-muscle cells. Plasma Ang II interacts with
endothelial cell and promotes the synthesis of vasodila-
tory agents; (ii) Ang II is a proinflammatory factor;
this is the result of oxidant stress induced by Ang II;
(iii) Ang II is a major trophic agent involved in
pathological vascular remodelling. A better under-
standing of these diverse effects of Ang II could lead
to novel indications for the use of converting enzyme
inhibitors and AT1 antagonists, particularly in the
prevention of atherosclerosis.

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In the past, based on inconsistent data, many authors reinforced the conclusion that available evidence was inconsistent and limited; therefore the case remains open whether CCB have adverse or beneficial effects on the risks of coronary heart disease, cancer, and bleeding.

In the meantime data in favor of a positive effect of CCB were published in the Systolic Hypertension in Europe (SYST-EUR) trial [3]. In this study a long-acting member of the dihydropyridine subclass of CCB was shown to reduce the rate of cardiovascular complications among elderly patients with isolated systolic hypertension. According to these data, the sixth report of the Joint National Committee [4] considered that isolated systolic hypertension was a compelling indication for the therapy with long-acting dihydropyridines. In 1998 the controversy reappeared with the publication of the results of the ABCD trial in the New England Journal of Medicine [5]. The appropriate blood pressure control in diabetes (ABCD) trial was a prospective, randomized, blinded trial comparing the effects of moderate control of blood pressure (target

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diastolic pressure 80–89 mmHg) with those of intensive control of blood pressure (target diastolic pressure, 75 mmHg) on the incidence and progression of complications of diabetes. The study also compared nisoldipine with enalapril as first-line antihypertensive agents. Analysis of the 470 patients in the trial who had hypertension showed a similar control of blood pressure, blood glucose and lipid concentrations with both antihypertensive drugs. Whereas, a significantly higher incidence of fatal and non-fatal myocardial infarction was found among those assigned to therapy with the CCB nisoldipine compared to those assigned to enalapril. The authors concluded that since the findings were based on a secondary endpoint, they required confirmation. This study prompted an editorial in the Lancet [6]; its authors concluded that until large randomized trials are completed, ACE inhibitors and low dose diuretics remain the preferred first-line agents for hypertensive patients with diabetes.

A few weeks ago the final results of the hypertension optimal treatment (HOT) trial have been published [7]. This trial included a total of 18,790 patients, aged 50–80 years, with hypertension and diastolic blood pressure between 100 and 115 mmHg who were randomly assigned to three different target diastolic blood pressure ≤90 mmHg, ≤85 mmHg and <80 mmHg. Felodipine, a long-acting dihydropyridine was given as baseline therapy in every patient with the addition of other agents, according to a five-step regimen. In addition 9399 patients were randomly assigned to 75 mg/day acetylsalicylic acid and 9391 patients were assigned to placebo.

The results of the HOT study demonstrate the benefits of lowering blood pressure in patients with hypertension to 140 mmHg systolic and 85 mmHg diastolic, or lower. Efforts to lower blood pressure further appear to give little further benefits but do not cause additional risk. Active lowering of blood pressure was particularly beneficial in the subgroup of 1500 patients with diabetes mellitus, confirming the importance of intensive treatment of this highly vulnerable population. On the whole, the rate of cardiovascular events seen during follow-up was much lower than that observed in previous prospective trials with diuretic or β-blocker therapy, probably as a consequence of the level of blood pressure control. At least these data provide assurance that claims of cardiac damage from CCB are not valid [8]. On the other hand, the HOT trial also showed that the association of a small dose of acetylsalicylic acid with active antihypertensive treatment reduced the risk of acute myocardial infarction without exaggerating the risk of cerebral bleeding. Clearer conclusions about the choice of blood-pressure-lowering drugs and their balances of risk and benefits for patients with diabetes as well as other groups of patients, will have to await the results of the current generation of randomized trials [9].

On the other hand, the capacity of CCBs to retard the progression of chronic renal failure remains to be elucidated [10]. The controversy on cardiovascular safety of CCBs has contributed to deny these drugs as first-step therapy in patients with chronic renal failure, in particular in those with diabetic nephropathy [11,12]. It is understandable, as stated by Pietro Zucchelli [11] and Robert Schrier [12], that because of their documented effects ACE inhibitors should be preferred as first line agents in patients with renal failure and hypertension. However, the contribution of CCBs to obtain the adequate control of blood pressure and proteinuria, used alone or in association with other antihypertensive agents remains to be elucidated [13]. An ongoing study, the Collaborative Study [14], will greatly contribute to answer this question. In this study a group of almost 1600 type 2 diabetic patients are being followed and treated in a double-blind fashion with irbesartan, amlodipine, or placebo. The goal of blood pressure control in this study is <130/85 mmHg, and the placebo arm will allow us to know the effectiveness of an adequate control of blood pressure per se.

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The clinical diagnosis of hypertensive nephrosclerosis—how reliable is it?

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Introduction

Mahomed was the first to suggest, in the late 19th century, that arterial hypertension might lead to renal scarring [1]. The concept of a ‘hypertensive nephrosclerosis’ was introduced by Volhard and Fahr in 1914 and has been extensively used in the literature since then. However, the very existence of a ‘hypertensive nephrosclerosis’ is still far from consensus. While it is indisputable that malignant hypertension is a definite cause of end-stage renal disease (ESRD), there remains a heated controversy as to whether ‘benign’ hypertension can also lead to ESRD. This discussion has been particularly intense in the last decade, during which data published by the United States Renal Data System (USRDS) has shown a steady increase in hypertension as a primary cause of ESRD.

Epidemiological data on hypertension as the presumed cause of end-stage renal failure

According to the USRDS, hypertension, together with diabetes and ageing, is one of the causes of the 7–11% per year increase in the number of new dialysis patients in the USA in the last decade [2]. In 1981, 10,991 of 47,183 patients (23%) were classified as having ESRD of hypertensive origin [3]. The prevalence of such patients increased to 28% in 1990 (46,618 of 166,371 patients). The corresponding incidence rates followed a similar pattern [3]. By the end of 1995, hypertension was the presumed cause of ESRD in 63,891 of 257,266 patients in chronic dialysis in the US (25% of the total) [2]. Accordingly, ESRD was attributed to hypertensive renal disease in 29% of a total of 305,876 new dialysis patients between 1991 and 1995 [2]. In African Americans with ESRD, hypertension was the leading diagnosis, corresponding to 36.8% of patients initiating dialysis during this period, as opposed to 26% in whites [2].

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Proteinuria appeared in 42% of these patients, while 18% eventually developed chronic renal failure and 7% developed malignant hypertension. Although this was an uncontrolled study, these figures were clearly higher compared to those found in the general population. Rostand et al. [10] analysed retrospectively the clinical evolution of 94 treated hypertensives over an average of 58 months. The frequency of deterioration of renal function at the end of this period was nearly 15%, even though diastolic pressure exceeded 90 mmHg in only a minority of patients. Rosansky et al. [11] carried out a retrospective study of 56 essential hypertensives and 59 normotensive controls, all of which exhibited nephrosclerosis was found in 40.6% of cases and proteinuria were excluded from the study. Renal arteriography was carried out in each patient to exclude artery stenosis. Histological analysis revealed ‘benign nephrosclerosis’ in 18.8% of patients, while malignant hypertension actually preceded renal injury. Although this was revealing the presence of exclusively vascular lesions. In most reports the diagnosis of hypertensive nephrosclerosis is made on exclusively clinical grounds, without renal biopsy or any effective demonstration that hypertension actually preceded renal injury. The insidious clinical manifestations of hypertensive nephrosclerosis may well mimic those of entities such as oligosymptomatic primary renal disease, renal atherosclerotic disease, cholesterol microembolization, and unnoticed episodes of malignant hypertension [13], the prevalence of hypertensive nephrosclerosis may actually be overestimated. Unfortunately, only a minority of clinical studies have included renal biopsies. Zucchelli and Zuccala [14] performed a careful prospective study, including renal biopsy, of 56 consecutive Caucasian patients clinically diagnosed as having hypertensive nephrosclerosis. Only in 48% of these cases was this diagnosis confirmed histologically, while 35% had actually atheromatous vascular disease, which might be the real cause of the progressive loss of renal function. There may be a closer agreement between clinical and histological diagnosis of hypertensive nephrosclerosis in African Americans, as shown by Fogo and co-workers [15]; in nearly 85% of these patients, renal histological examination was consistent with the clinical diagnosis by revealing the presence of exclusively vascular lesions. We have recently reported in preliminary form the results obtained in 64 consecutive hypertensive patients with serum creatinine in excess of 1.5 mg/dl, that were biopsied between 1988 and 1997 in São Paulo, Brazil [16]. Patients with secondary hypertension or massive proteinuria were excluded from the study. Renal arteriography was carried out in each patient to exclude artery stenosis. Histological analysis revealed ‘benign nephrosclerosis’ in 18.8% of patients, while malignant nephrosclerosis was found in 40.6% of cases and primary renal disease in the remaining 40.6%.

The true dimension of the problem

Although the scarce available histological evidence does suggest that ‘hypertensive nephrosclerosis’ is quite often a misdiagnosis, a substantial fraction of hypertensive patients, which varies with ethnic, socioeconomic, and environmental factors, appears to suffer from true hypertensive nephrosclerosis. Even if only a small percentage of these patients eventually develops ESRD, the consequent demand for replacement therapy will be considerable given the high prevalence of hypertension, and will tend to increase as survival of these patients improves. Even though the dramatic events resulting from cerebrovascular and coronary injury are still likely to capture most of the public attention, the personal and socioeconomic burden imposed by the more insidious renal complications of hypertension cannot be ignored.

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Clostridium difficile and antibiotic-associated diarrhoea—importance of C. difficile for the nephrologist

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Clostridium difficile-associated diarrhoea (CDAD) is particularly likely to occur, and be more severe, in elderly and/or immunosuppressed patients [1,2]. It is also a common problem in hospital units in which there is a high level of antibiotic use [3]. These factors are likely to pertain to most nephrology and/or renal transplant units. Indeed, chronic renal failure has been identified as an independent risk factor for severe CDAD [4].

Epidemiology and pathogenesis

CDAD is intimately linked to antibiotic use, though it can occur following the use of some antineoplastic drugs that have inherent antibiotic activity [5] and can occur up to 8 weeks after even a single dose of any antibiotic [6]. The risk is greatest with broad spectrum beta-lactam agents. Second and third generation cephalosporins, broad spectrum penicillin derivatives and clindamycin are the most frequently implicated drugs [7].

CDAD is caused by an overgrowth of toxin-producing C. difficile within the large bowel. Non-toxigenic strains are not considered pathogenic. The proportion of C. difficile strains that are toxigenic range from 75% to 90%, with higher rates among hospital strains, compared to those in the community [7]. Both toxigenic and non-toxigenic strains may be carried in the large bowel asymptotically. Up to 5% of the general adult population may carry the organism, with carriage rates of 10–30% among hospitalized patients. A recent report suggests that asymptomatic carriage, of either toxigenic or non-toxigenic strains, protects against subsequent symptomatic CDAD [8].

Clinical features of CDAD

Most patients (75–85%) with antibiotic-associated diarrhoea are not infected with C. difficile. Such patients develop a mild, self-limiting diarrhoea that is rarely associated with abdominal pain or constitutional symptoms. Of the remaining 15–25%, who are infected with C. difficile, many will still have a relatively mild illness. CDAD is caused by an overgrowth of toxin-producing C. difficile within the large bowel. Non-toxigenic strains are not considered pathogenic. The proportion of C. difficile strains that are toxigenic range from 75% to 90%, with higher rates among hospital strains, compared to those in the community [7]. Both toxigenic and non-toxigenic strains may be carried in the large bowel asymptotically. Up to 5% of the general adult population may carry the organism, with carriage rates of 10–30% among hospitalized patients. A recent report suggests that asymptomatic carriage, of either toxigenic or non-toxigenic strains, protects against subsequent symptomatic CDAD [8].

Heat-resistant spores produced by C. difficile allow the organism to survive in the hospital environment. The immediate environment around a patient with CDAD can be heavily contaminated with these spores [9]. This allows for ready transmission to other patients, usually on the hands of health care workers [10]. Although most commonly associated with hospitals, CDAD can be community acquired in up to one quarter of cases [11]. The increasing incidence of such cases is probably linked to the escalating use of broad spectrum oral antibiotics in the community.

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Diagnosis

Because *C. difficile* may be carried asymptomatically, isolation of the organism from stools does not automatically imply that the patient has CDAD. Direct detection of *C. difficile* toxin in stool has become the standard method of diagnosis. The tests used are rapid (typically requiring 2–4 h) and specific. They have reported sensitivities of 63–94% and specificities of 75–100% [6,9]. Two negative stool toxin assays virtually rules out a diagnosis of CDAD.

Sigmoidoscopy is useful for diagnosing severe CDAD, where characteristic pseudomembranes may be seen in 51–55% of cases [9]. However, macroscopic changes seen in milder forms are non-specific and are difficult to distinguish from other causes of colitis.

There is no role for screening of asymptomatic patients for the presence of *C. difficile* or for further testing of stools in patients who have responded to therapy for CDAD.

Therapy

Most patients with antibiotic-associated diarrhoea do not have CDAD and therefore do not require specific antibiotic therapy. Even in those infected with *C. difficile*, 20–25% will respond to withdrawal of the causative antibiotics alone. With the availability of rapid, sensitive toxin assays from stool, empiric therapy for CDAD without diagnostic testing is inappropriate.

There are advantages to avoiding therapy in mild cases of CDAD. It has been shown that patients who receive specific therapy for CDAD have a higher rate of relapse than those who respond to discontinuation of antibiotics alone. In addition the drugs used to treat *C. difficile* (metronidazole and vancomycin) are both associated with the emergence of vancomycin-resistant enterococci [12].

Who should be treated? Unfortunately there are no evidence-based clinical guidelines to aid the clinician in this decision. The first step in treatment is to discontinue any current antibiotic therapy, if possible. Patients who have abdominal pain, tenderness, fever, constitutional symptoms or profuse diarrhoea should receive specific therapy directed against *C. difficile*. For haemodynamically stable patients with mild to moderate diarrhoea, without the above signs or symptoms of severe CDAD, it is reasonable to monitor them for 48–72 h. Therapy should only be started if there is no improvement in clinical status over this time.

Initial therapy

Oral metronidazole and oral vancomycin are the two most frequently used agents for CDAD. In comparative trials they have been found to be equally effective. However, vancomycin may be associated with higher rates of relapse of CDAD and emergence of vancomycin-resistant enterococci, as well as being considerably more expensive. Metronidazole may not be tolerated by every patient and it should be avoided in pregnancy. In either case the drugs must be given orally (to achieve sufficient concentrations within the bowel lumen). A 10-day course of either agent is usually sufficient, though it may take 2–4 days for a clinical response to be seen. Shorter courses may be associated with a higher relapse rate.

Severe cases of CDAD, which may be associated with ileus, pose greater therapeutic problems. Some success has been reported with intravenous metronidazole, which can enter the bowel via biliary excretion. Either agent can be given directly into the bowel via a retention enema, colostomy or small bowel feeding tube. There is no role for intravenous vancomycin, which does not enter the bowel lumen.

Patients with severe disease should have an early surgical opinion. In one study 5% of patients with CDAD required surgical intervention [13]. This figure is likely to be higher in nephrology patients with CDAD. Reported attributable mortality in this subgroup ranges from 14 to 38% [14].

Recurrent episodes

Relapse of CDAD occurs in up to 20% of patients who have received treatment for CDAD. Most patients will respond to a second 10-day course of metronidazole or vancomycin. A number of novel biotherapies have been reported for treating and preventing further relapses. To date the only therapy shown to reduce the rate of further relapses in a randomized control trial is the yeast *Saccharomyces boulardii*. A dose of 500 mg twice daily orally, starting 4 days before the end of a 10-day course of specific antibiotic therapy and continued for 1 month, has been shown to reduce the rate of further relapses by 50% [15]. There are anecdotal reports of the use of other biotherapies, such as live yoghurt, *Lactobacillus* and brewer’s yeast.

Prevention of CDAD

Antibiotic control

Avoiding unnecessary antibiotics, and excessive duration of antibiotic therapy, are the most important measures for preventing CDAD. In particular, overuse of second and third generation cephalosporins and broad spectrum penicillin derivatives should be avoided. Antibiotics should be used with caution in any patient who has had CDAD in the previous 2–3 months as they are likely to still be colonized with *C. difficile* and therefore prone to relapse.

There is no role for prophylactic antibiotic therapy for CDAD. Treatment of asymptomatic carriers may increase the risk of symptomatic CDAD.
Anaemia in the patient with renal insufficiency: documenting the impact and reviewing treatment strategies

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Introduction

The care of patients in the early phases of progressive renal insufficiency has received increasing attention over the past decade, as there is an increased recognition that much of the comorbidity seen in dialysis patients exists prior to the initiation of dialysis. Anaemia has been identified as an important predictor of morbidity and mortality in the dialysis population [1–3]; however, there are only a few studies addressing anaemia therapy specifically in the population with progressive renal insufficiency.

In an attempt to clarify some of the issues, this editorial will address the definition of anaemia in the context of early renal insufficiency, and the impact of anaemia in patients with renal insufficiency not yet on dialysis, and will review the evidence to date about the treatment of anaemia in this patient group.

Defining anaemia in the patient with renal insufficiency

The definition of anaemia in patients with renal insufficiency is problematic. While in all other realms
of medicine we define anaemia as that level of haemoglobin which is below the normal physiological range (normal ranges for haemoglobin for men are between 130 and 160 g/l, and in women are between 120 and 140 g/l), as nephrologists, either clinical or investigative, we define ‘renal’ anaemia with no regard to gender differences, and only begin treatment at absolute haemoglobin levels lower than 100 g/l. Target haemoglobins continue to be below or at the lower level of gender-matched physiological levels (i.e. 120 g/l). It may be that funding issues and previous notions about the potential detrimental effects of higher haematocrit in dialysis patients have led us to define anaemia in this way. However, in light of newer information, we may need to re-examine previous practices. The impact of anaemia and of falling haemoglobin levels over time have been studied in a prospective cohort study involving eight Canadian tertiary care centres. At levels of haemoglobin currently suggested as ‘target values’ for dialysis patients, persons with early renal insufficiency demonstrate left ventricular hypertrophy [4]. Furthermore, patients who demonstrate a fall in haemoglobin level within that same current ‘target range’ (115–125), or at higher haemoglobin levels, have an increased risk of left ventricular growth over a 12-month period (odds ratio 1.320 for each 5 g/l decrease in haemoglobin, CI 1.10–1.59, \( P_{0.004} \)) [5]. The acceptance and operational definition of ‘renal’ anaemia as a haemoglobin level of less than 100 g/l, exposes renal patients to a non-physiological state for extended periods of time prior to renal replacement therapy. Further descriptions of the true burden of illness for this population at different haemoglobin levels would help to identify critical points for intervention strategies. A first step towards quantifying this burden is to accept that anaemia in patients with renal insufficiency is defined as that level of haemoglobin below gender specific normal ranges.

The impact of anaemia in patients with renal insufficiency

There is ample documentation of the adverse impact of anaemia in dialysis patients. Anaemia has been associated with ischaemic heart disease, left ventricular hypertrophy, and with impaired quality of life and exercise tolerance [2,6]. Furthermore, there are data to support poorer outcomes of dialysis patients in terms of hospital days and mortality [1,7,8]. Numerous publications have demonstrated the positive impact of raising haemoglobin [6,7,9]. Thus the importance of treating severe anaemia in dialysis patients is not disputed.

There are limited data, however, about the impact of and the successful treatment of anaemia in patients not yet on dialysis. Treatment regimens with erythropoietin, with and without iron therapy, have demonstrated improvements in quality of life, symptoms of fatigue, and cardiovascular parameters [10–14]. Studies in children have suggested, that reversing anaemia leads to regression of left ventricular hypertrophy [15].

The greatest concern has been that increasing the haemoglobin in patients with progressive renal decline would lead to accelerated rates of renal decline. Early studies by Garcia et al. and Meyers et al. had demonstrated adverse effects of elevated haematocrit on renal function in rat models of renal insufficiency [16,17]. However, in those animal studies, blood pressure was not well controlled. Thus, the presence of severe hypertension in the treated (non-anaemic) animals negated any firm conclusion about the impact of elevated haematocrit alone on rate of renal decline.

To date, a small number of studies have attempted to address this question in human subjects directly. Teehan et al. evaluated the impact of erythropoietin therapy on 83 predialysis patients in a randomized controlled study. These investigators demonstrated improvement in haemoglobin and no acceleration of renal decline [12]. Interestingly, studies by Kramar et al. in children and by Kuriyama et al. in adults suggested that patients with stable haemoglobin, or those receiving erythropoietin have improved well-being and slower rates of renal deterioration than matched controls [18,19]. The studies available to date demonstrate at worst no impact on renal decline, and at best a slowing of renal decline, with anaemia therapy. In the studies cited above, many patients had significantly impaired renal function, with mean values as low as 10 ml/min, which could now be considered the level at which one commence dialysis [20]. Thus the impact of higher haemoglobin on the course of renal deterioration early in the course of disease is still not well known. To date, there have been no human studies corroborating declining renal function as a consequence of rising haemoglobin in humans; thus, for most clinicians this point against treatment of anaemia should be moot.

Anaemia therapy: why and how

The goal of anaemia therapy is to alleviate those symptoms or conditions attributable to anaemia; thus, in the current era of responsible use of health care funding and resources, it is important to monitor these goals in both individual patients and in populations.

Anaemia therapy in patients with renal insufficiency has been demonstrated to improve cardiovascular parameters, exercise tolerance, and quality of life [10,12–14]. Given the paucity of randomized control trials the current published data do not permit definitive statements recommending the treatment of anaemia to prevent renal decline or to reduce cardiovascular risk (e.g. prevention or attenuation of left ventricular hypertrophy). Studies specifically addressing these issues are currently under way.

Based on theoretical grounds, the consistent data from uncontrolled trials and small randomized controlled trials, as well as data from the dialysis population, we can develop a logical treatment plan for the
anaemia of progressive renal insufficiency. Initially, it is recommended to search for and identify any secondary causes of anaemia (iron, folate or B12 deficiencies). It is becoming more evident that a similar ‘iron-responsive’ anaemia to that seen in dialysis patients is present in patients not yet on dialysis, and even when not receiving erythropoietin therapy. Silverberg et al. described increases in haemoglobin with intravenous iron saccharate supplementation in ‘predialysis’ patients without erythropoietin therapy [21]. Similarly in our renal clinic, approximately 65% of all patients have an iron-responsive anaemia at very moderate levels of renal impairment (creatinine clearances \( \sim 40-50 \text{ ml/min} \) (unpublished data). These patients have a documented decrease in haemoglobin level, normal serum ferritin levels, transferrin saturation values below 20, no evidence of blood loss, and respond to either oral or intravenous iron supplementation. The only known source of iron loss in these patients is lack of iron-rich protein sources. Iron responsiveness is therefore defined as a stabilization or rise of haemoglobin, and/or rise in transferrin saturation in association with iron therapy.

However, as in the dialysis populations, the most usual cause of anaemia in progressive renal insufficiency patients is a relative erythropoietin deficiency. Thus, definitive therapy for the anaemia in this population must necessarily include erythropoietin. Close attention to blood-pressure control, rate of rise of haemoglobin, and to the development of true iron deficiency is recommended.

The escalating costs of treatment of all patients with renal disease may make advocating the use of expensive medication (e.g. erythropoietin) in the progressive renal insufficiency population problematic. While there is ample evidence that treatment of anaemia of dialysis patients reduces morbidity and resource utilization [7,8], extrapolation of these findings to patients with progressive renal insufficiency requires further validation. Anaemia therapy may improve well-being, appetite, and subsequent nutritional status or, perhaps more importantly, slow the rate of renal deterioration, all of which may delay the initiation of dialysis. The cost savings alone of this ‘delay’ in saved dialysis months (i.e. (in Canadian dollars) \( \sim $600/\text{month of erythropoietin vs}\ $3300/\text{month of dialysis therapy} \) could justify the use of the drug in this population. It remains for well-designed long-term studies to demonstrate that early treatment of anaemia in patients with renal insufficiency results in a reduction in rate of renal decline, reduction in cardiovascular disease or morbidity, or in improved dialysis outcomes. The optimal timing of anaemia therapy also needs to be determined for this particular group of patients.

Summary

This paper attempts to present a context in which nephrologists can re-evaluate definitions of acceptable haemoglobin levels in renal populations, and re-examine previous notions about the impact of relative and absolute anaemia on patients with progressive renal insufficiency. Also, the nephrology community needs to examine rigorously treatment strategies aimed at reversing anaemia specifically in this population. Data are presented to support the notion that anaemia is disadvantageous to the patients with progressive renal insufficiency, and does need to be treated.

The ongoing poor prognosis of patients receiving renal replacement therapy may well be due to our previous inattention to this correctable cause of morbidity early in the course of progressive renal disease. Long-term studies addressing these important clinical issues need to be supported, and evaluated within both immediate and future economic implications.

References

Familial aggregation of end-stage renal failure: aetiological implications

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Introduction

The family history often yields clues to the presence of both inherited and environmentally induced illnesses. When appropriate epidemiological and biochemical analyses are applied to the familial clustering of a disease, we have the potential better to understand its pathogenesis. This editorial reviews the familial clustering of end-stage renal disease (ESRD). The data provide strong evidence in support of an inherited susceptibility to renal failure that occurs independently from the systemic processes of hypertension, diabetes mellitus and connective tissue disease.

African Americans

In 1988, Ferguson et al. observed the familial aggregation of diabetic- and hypertension-associated ESRD in blacks residing in Los Angeles, California [1]. In this report from a large urban area, blacks who had first or second degree relatives on haemodialysis were found to be at 5-fold increased risk of development of subsequent ESRD compared with blacks without a positive family history. We confirmed and extended this observation in a small southeastern city. Blacks residing in the southeastern US have among the highest incidence rates of ESRD of all Americans. Approximately 1 in 1500 blacks from this high risk region develop ESRD [2]. Strikingly, 40% of black patients with hypertension and 35% with type II diabetes mellitus-associated ESRD residing in Winston-Salem, North Carolina reported having close relatives on dialysis [3]. This contrasts with chronic forms of glomerulonephritis and type I diabetes mellitus-associated ESRD, diseases with known genetic predisposition, where only 13–17% of black index cases with ESRD reported having relatives with ESRD. In North Carolina, blacks with a first degree relative on haemodialysis were at 9-fold increased risk of developing subsequent ESRD compared with age-, sex- and race-matched controls [3]. As in Los Angeles, blacks from North Carolina with first or second degree relatives on dialysis were at 5-fold increased risk. As in other racial and ethnic groups, family history of nephropathy in type II diabetes mellitus is a strong predictor of whether a black diabetic is at risk of subsequent renal failure [4] (see section on Caucasians, below).

We reported that multiply affected black families with ESRD from North Carolina often contained members with disparate aetiologies of chronic renal disease [3]. These families included members whose renal failure could be attributed to hypertension, diabetes mellitus types I and II, idiopathic and systemic glomerular diseases and human immunodeficiency virus (HIV)-associated nephropathy. This observation has been confirmed throughout the US. Bergman et al. in Birmingham, Alabama, reported that in 70% of families, first degree relatives of black hypertension-associated ESRD index cases had either proteinuria, elevated serum creatinine concentration or ESRD [5]. Strikingly, 50% of the first degree relatives with ESRD from these carefully evaluated, non-diabetic index cases had diabetic nephropathy. Simon et al. reported that 28% of blacks with HIV-associated ESRD from a national dialysis network had close relatives with ESRD [6]. None of the relatives on dialysis were HIV positive, confirming disparate aetiologies of ESRD in these families. Similarly, we reported that 28% of blacks with systemic lupus erythematosus (SLE)-associated nephritis had relatives with ESRD [7]. In nearly all cases, their relatives with ESRD lacked any evidence of SLE or collagen vascular disease.

Bergman et al. also measured blood pressure and glomerular filtration rate (GFR) in first degree relatives.
of blacks with hypertension-associated ESRD [8]. These relatives had reduced GFRs and elevated blood pressures despite normal urinalyses and serum creatinine concentrations. The reduced GFR was unrelated to fasting glucose:insulin ratio or body mass index. This study suggests that a primary renal disease probably preceded the development of hypertension in these families.

**Caucasians and native Americans**

The incidence rates of the common aetiologies of ESRD are lower in American whites than blacks [2]. The familial clustering of renal failure is also less marked in the white population [9,10]. In North Carolina, the risk of ESRD in first degree relatives of white dialysis patients was increased nearly 3-fold compared with the general white population [10]. The age at ESRD onset within white families was also highly correlated [10].

In whites, familial aggregation of ESRD occurs mainly in diabetic- and glomerulonephritis-associated ESRD and not in the less well defined syndrome of hypertension-associated renal disease. It is apparent that the major risk factor for developing overt diabetes mellitus-associated nephropathy, in type I or type II disease, is the presence of close relatives with renal failure [11,12] or parents with hypertension [13].

Familial aggregation of renal disease has also been observed in Pima Indians with type II diabetes [14]. Familial history of nephropathy or hypertension in parents is a more important predictor of diabetic ESRD than is poorly controlled blood sugar or hypertension [11]. Approximately 30% of white diabetics are at risk of nephropathy, and this rate can be reduced to 10% or the onset of nephropathy delayed, with strict blood sugar and glycaemic control [15]. Importantly, even with non-intensive medical management, 70% of diabetics never develop nephropathy. It has been proposed that the 30% rate of renal disease in diabetes reflects the maximal genetic effect, when the environmental factors (glycaemic control and blood pressure) are not controlled intensively [15]. Increased levels of proteinuria have also been observed in the non-diabetic, normotensive offspring of type II diabetic patients with nephropathy [16]. This further demonstrates the independence of renal disease and hyperglycaemia.

Chronic glomerular diseases are known to aggregate in families [17]. To date, IgA nephropathy [18] and focal and segmental glomerulosclerosis (FSGS) [19] have been best studied. The identification of linkage between polymorphic markers on chromosome 19 and FSGS in a large, multi-generational white American kindred provided unequivocal evidence of a genetic component in this illness [20]. These linkages have not yet been confirmed in other families or racial groups.

**Aetiological implications**

Familial clustering of a disease does not prove whether environmental exposure, inherited factors or an intervention between the two is causative. Segregation analysis is most useful in that regard. Unfortunately, these studies have not yet been performed in ESRD. The similar rates of familial aggregation of ESRD that have been observed in blacks from socially and geographically distant regions in the US suggest that genetic factors are involved [1,3,5].

Lei et al. recently performed a population-based case-control study of the familial aggregation of ESRD [21]. They wanted to determine whether an excessive prevalence of renal disease risk factors within certain families, predominantly hypertension and/or diabetes, could account for the clustering of ESRD. They performed multiple linear regression analyses controlling for the proband’s age, gender, race, family size, socioeconomic status and personal and family history of hypertension and diabetes. They concluded that the familial risk of ESRD was in excess of that predicted solely from the clustering of hypertension and diabetes within families [21]. Although this study did not conclusively implicate genetic factors in the development of ESRD, the familial clustering was most marked in families having at least three affected members. The authors’ interpretation was that genetic factors were most likely to cause ESRD in families with larger numbers of affected relatives [21].

It is highly unlikely that the observed familial aggregation of ESRD is caused solely by environmental factors. The λs, or the risk of ESRD developing in siblings of black index cases with ESRD compared with the risk in the overall black population, is nine [3]. The λs provides an estimate of the genetic contribution to a disease, which increases as the λs rises. In diabetes mellitus-associated ESRD in blacks, we calculated the λs to be 10 [4]. This is higher than the risk that siblings of type II diabetics will contract diabetes mellitus compared with the general population. Lifton et al. reported λs values of 33–45 in blacks with early-onset ESRD [22].

An animal model of renal failure strongly supports the observations that we and others have made in human ESRD. The Fawn-hooded rat is an animal model of hypertension-associated renal disease that develops FSGS. Brown et al. reported that two genes on rodent chromosome 1, termed Rf-1 and Rf-2, made major contributions to the development of glomerulosclerosis and proteinuria [23]. These markers were distinct from those linked to hypertension in this inbred strain of rats. This model strongly supports the notion that ‘renal failure genes’ exist and are independent from the genes that contribute to high blood pressure.

In conclusion, I believe that it is appropriate to view susceptibility to the common aetiologies of human renal disease as having a major genetic component. This would explain why select hypertensives, diabetics and patients with SLE or HIV infection are more likely than others to develop ESRD. It is my hope and expectation that genetic markers for ESRD susceptibility ultimately will be identified. We will then be able to determine the protein products of these ‘renal failure genes’. These products will enhance our understanding...
of the pathogenesis of renal failure and could yield novel treatment strategies. Until these genes are identified, it would be prudent for physicians caring for hypertensive and diabetic patients to identify those having relatives with nephropathy. Hypertension, hyperlipidaemia and diabetes mellitus should be treated aggressively in these individuals at high risk of developing future renal disease.

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Vascular steal syndrome and ischaemic monomelic neuropathy: two variants of upper limb ischaemia after haemodialysis vascular access surgery

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Introduction

Distal ischaemia following placement of upper limb arterio-venous accesses for haemodialysis occurs with widely varying frequency depending on surgical tech-
Diabetic haemodialysis patients are at increased risk of upper limb ischaemia after access surgery because of often severe digital calcific atherosclerosis and pre-existing diabetic neuropathy. Accesses originating from the brachial artery are also a major predisposing factor, as this vessel constitutes the sole arterial inflow to the forearm and hand, and in the absence of collateral vessels about the elbow, diversion of all or most of high flow brachial arterial blood through an access will produce distal ischaemia.

Vascular steal syndromes

In mild cases of vascular steal, the onset is insidious and often delayed for days, weeks or months. Symptoms include numbness, painful paraesthesia, stiffness and swelling of one or more fingers, and are sometimes precipitated by, or exacerbated during haemodialysis. Intra-dialytic lowering of systemic blood pressure or pO$_2$ may explain the dialysis-associated symptom exacerbation [7]. The radial pulse is usually present. Symptoms may resolve spontaneously over weeks or months.

In more severe cases, numbness and pain progress and are associated with pallor, coolness, diminished sensation, ischaemic ulcers, trophic changes and progressive dry gangrene of one or more digits (Figure 1). The radial pulse is absent. In very severe cases of vascular steal, changes are apparent on the operating table with immediate pain, pallor, pulselessness, and paralysis of the hand.

The pathogenesis of vascular steal with a side-to-end radiocephalic fistula is shown in Figure 2. The low pressure run off system afforded by the fistula causes reversal of blood flow from digital and palmar arch arteries through the distal limb of the radial artery. In patients with pre-existing athero-occlusive narrowing of the palmar arch arteries and their tributaries, even mild degrees of flow reversal may result in clinically significant steal. In patients with normal palmar arch arteries, more severe degrees of flow reversal would be necessary to produce clinical symptoms. End-to-end rather than end- or side-to-side fistulae are therefore preferred in order to eliminate the distal arterial limb through which retrograde flow occurs. In the brachial location, end-arterial fistulae are not possible, hence the distal brachial arterial limb and its tributaries provide conduits for flow reversal.

Vascular steal syndromes can usually be diagnosed clinically. Cardinal findings are symptom relief and reappearance of the radial pulse with manual occlusion of the venous limb of the access (abrogating retrograde flow). When physical symptoms and signs are early, mild or atypical, and the diagnosis uncertain, Doppler ultrasound studies showing severe flow reversal and digital plethysmography (pulse volume recordings (PVRs)) documenting digital pressures <50 mmHg, and digital-brachial indices <0.47 [8] with symptom relief and augmentation of the pulse wave with fistula compression, are diagnostic. Fistulography is indicated in cases of severe hand ischaemia after access surgery, as it may show potentially removable athero-occlusive or embolic arterial disease with or without the presence of retrograde arterial flow and coexisting clinical steal syndrome [9]. It is important to note that demonstration of retrograde arterial flow does not predict or

Fig. 1. Severe steal syndrome 3 months after insertion of a brachiocephalic polytetrafluoroethylene loop graft. There is a non-healing ischaemic ulcer of the forefinger, established dry gangrene of the middle finger, and discolouration and blister formation at the tip of the fourth finger. Graft closure and amputation of the middle finger were performed.

Fig. 2. Schematic diagram showing pathogenesis of vascular steal in a side-to-end radiocephalic fistula. A, cephalic vein; B, fistula anastomosis; C, distal limb of radial artery responsible for steal; D, ligated distal radial arterial limb preventing retrograde blood flow.
indicate existence of a clinical steal syndrome. Retrograde blood flow is a physiologic consequence of the rheology of an arteriovenous access, and up to 67% of radiocephalic fistulae evaluated by extravascular electromagnetic flowmetry [10], and 86% of proximal arteriovenous grafts evaluated by digital plethysmography [8], show clinically silent retrograde flow. Digital pulse oximetry is also useful in diagnosing steal syndromes [5]: in 5 patients with side-to-side arteriovenous fistulae, symptoms suggestive of steal, yet normal physical examination, arterial oxygen saturations were low in all cases and rose to normal levels (>90%) with fistula compression.

Treatment of vascular steal

Severe cases of vascular steal require ligation or removal of the access. Ligation of the distal radial limb of a side-to-side radiocephalic fistula (Figure 2) is curative. Various techniques of fistula banding [4,11] may also be used, but there is risk of subsequent access thrombosis. Ligation of the arterial limb just distal to the access and placement of an interposition graft from the proximal arterial inflow to a more distal artery is technically demanding but often successful [4].

No reliable predictors of development of a steal syndrome exist. Allen’s test documents patency of the ulnar artery, and should be performed prior to placement of radiocephalic fistulae. The patient is instructed to clench and release his fist several times, then to make a tight fist so that venous blood is forced from the palm. The radial and ulnar arteries are manually occluded by the examiner until the palm blanches. The ulnar artery is released, and the palm should flush immediately if arterial inflow through this vessel is intact. The test however, is applicable only to radiocephalic fistulae, and may be falsely negative in the 9–20% of the population with aberrant upper limb arterial anatomy. Further pre- or intra-operative evaluation is warranted in patients deemed to be at high risk based on prior steal syndromes, known peripheral vascular disease, advanced age, or presence of diabetes.

A systolic blood pressure difference in the upper limbs of >20 mmHg, and intra-operative digital-brachial indices <0.47, or digital pressures <50 mmHg are suggestive, but not absolutely predictive of vascular steal [8]. Intraoperative monitoring of digital oxygen saturation may prove useful in guiding the anastomotic size of arteriovenous fistulae and graft, and in banding operations [12].

Ischaemic monomelic neuropathy

Ischaemic neuropathy of upper limb nerves after dialysis access surgery was first reported by Bolton in 1979 [13]. A more detailed description of the condition and coining of the term ischaemic monomelic neuropathy (IMN) came in 1983 [14]. Subsequent reports have remained confined to neurologic and surgical literature [15–17] so that under- and mis-diagnosis of IMN is frequent in the realm of renal medicine. The condition is rare, and precise incidence figures are not available from existing reports. IMN is seen almost exclusively in diabetic haemodialysis patients [18], particularly older ones, with pre-existing peripheral neuropathy and/or peripheral vascular disease. Acute pain, weakness and paralysis of the muscles of the forearm and hand (often with prominent sensory loss and dysesthesiae) occur immediately (within minutes to hours) of placement of an arteriovenous access in the brachiocephalic or anteceubital location. The condition is not seen with accesses originating distal to the brachial artery. IMN results from sudden diversion or transient occlusion of the blood supply to the nerves of the forearm and hand, the acute ischemic insult being severe enough to damage nerve fibres, but insufficient to produce necrosis of other tissues. The condition may therefore be most simply described as a steal syndrome affecting only the nerves. This selective neural injury may be due to the greater metabolic requirements and more tenuous blood supply of peripheral nerves when compared to other tissues [19]. The anteceubital area may also be the ‘watershed area’ for the vasae nervorum of the three upper limb nerves [20].

IMN can be diagnosed clinically based on immediate symptom onset and dominant neurologic symptoms and signs. The hand is warm, though the radial pulse is variably present. There are no signs of muscle infarction such as tenderness or pain with passive extension; and signs of ongoing vascular insufficiency and trophic changes are usually absent. Features differentiating IMN from vascular steal syndrome are shown in Table 1. Nerve conduction studies show axonal loss and reduced sensory and motor nerve conduction velocities of median, radial and ulnar nerves [12]. One study reports a predilection for earlier and more severe (but not isolated) median nerve involvement [21]. Electromyography reveals severe acute denervation of all upper limb nerves which is maximal distally [13,16]. Digital pressures are >50 mmHg and digital-brachial pressure indices >0.3

| Table 1. Differentiating vascular steal syndrome from ischemic monomelic neuropathy |
|------------------------------------------|----------|----------|
| **Onset**      | Steal syndrome | IMN       |
| **Predilection for diabetics** | usually insidious | acute    |
| **Access location** | wrist, forearm, upper arm | forearm, upper arm |
| Skin affected  | skin > muscle > nerve | nerve     |
| **Degree of ischaemia** | severe, diffuse | mild-moderate |
| **Radial pulse present** | −−−−− | −−−−− |
| **Digital pressures** | −−−−− | −−−−− |
| **Reversibility** | ±±±± | ±±±± |

The antecubital area may also be the ‘watershed area’ for the vasae nervorum of the three upper limb nerves [20].
Fistulography is indicated in cases where there is clinical uncertainty and in search of correctable embolic or athero-occlusive disease of the inflow or distal arteries [9].

Differential diagnosis of IMN

IMN may be misdiagnosed as a complication of axillary block or patient positioning during surgery; or attributed to post-operative or psychogenic pain. Involvement of a single upper limb nerve excludes the diagnosis of IMN. Paralysis of a single nerve in the setting of vascular access surgery should prompt a search for local nerve compression secondary to haematoma, aneurysm or abscess [22]. Some cases of carpal tunnel syndrome may also manifest or exacerbate following access surgery, perhaps related to oedema and venous hypertension in the area of the flexor retinaculum, or to a component of vascular steal [23,24]. It is unlikely that cases of ipsilateral carpal tunnel syndrome after access surgery are related solely to the access, either via ischaemic neuropathy or steal syndrome. In early reports of CTS in association with haemodialysis accesses, the onset of CTS was one or more years after access surgery [25,26], and retrospective staining of transverse carpal ligament biopsies revealed beta-2-microglobulin amyloid in half of the cases in one report [25].

Treatment of IMN

Immediate closure of the access is required upon diagnosing IMN in order to prevent severe and irreversible neurologic injury. Even with early access closure, paralysis and pain may be permanent or only partially reversible [15–17]. Delay in diagnosis will of course reduce the likelihood of improvement, hence recognition of this uncommon complication of vascular access surgery by surgeons and nephrologists is crucial.

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References

Transplantation strategies in type 1 primary hyperoxaluria: the issue of pyridoxine responsiveness

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Introduction

Type I primary hyperoxaluria (PH1) is a rare inborn error of oxalate metabolism, characterized by the absence or deficiency of the liver peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT), which promotes the transamination of glyoxylate to glycine, using pyridoxal phosphate as coenzyme [1]. The accumulated glyoxylate is either oxidized to oxalate or reduced to glycolate, leading to hyperglycolic hyperoxaluria. Recent works have shown that there is considerable genetic heterogeneity of the AGT defect in PH1, which corresponds to a great clinical variety in presentation and progression of the disease [2]. There is a subset of patients in which PH1 presents in infancy with end-stage renal failure (ESRF) due to nephrocalcinosis [3]. Most commonly, the disease is characterized by severely recurrent nephrolithiasis, which begins early in life and leads to ESRF within the first two decades [4]. In a minority of the patients, a milder course with late onset of ESRF has been reported [5]. It is presumed, though not definitely established, that in the latter patients the mutant AGT is associated with residual enzymic activity, and this has been related to pyridoxine responsiveness [6]. Unfortunately, identification and differential diagnosis of PH1 are often disregarded in this subset. Furthermore, while at earlier stages of the disease pyridoxine responsiveness can be assessed easily by measuring oxalate excretion on and off treatment, with the onset of ESRF and anuria this is no longer sufficient and more complex procedures become necessary.

Pyridoxine sensitivity is important for the management of patients with PH1 since responsiveness to and supplementation of pyridoxine may prevent or delay the progression to ESRF. Likewise, in the setting of ESRF, the type of response to pyridoxine may help in the choice of transplantation strategies, indicating which patient could be eligible for isolated kidney and which for combined liver–kidney transplantation.

This editorial comment will discuss diagnostic criteria and guidelines to assist in the choice of transplantation strategies in PH1.

The diagnostic work-up

The preliminary discrimination between different types of hyperoxaluria relies on the assessment of associated abnormalities in generation and urinary excretion of metabolically related substances: PH1 is identified through the accompanying hyperglycolic aciduria. In patients with ESRF, detection and differentiation of PH are accomplished by assaying relevant chemistries in blood and dialysis fluids [7]. At any level of renal function, the point concerning pyridoxine responsiveness deserves special attention. This can be ruled out by challenging patients with pyridoxine (5–10 mg/kg body weight/day), which restores oxalate and glycolate levels to normal within a few weeks. Since most of these patients are referred to as having residual AGT activity on liver biopsy [3], it is advisable to assay AGT on liver biopsy in all PH1 patients. This procedure should be mandatory in those being considered for any transplantation strategy. In patients with ESRF, some prediction of occurrence and extent of calcium oxalate deposits is highly important, because the function of grafted kidneys is crucially dependent on the burden of body oxalate. Measurement of plasma oxalate and estimation of calcium oxalate saturation are useful to decide the timing and choice of transplantation strategy. Current data support evidence for plasma oxalate exceeding 50 μmol/l being associated with the risk of calcium oxalate accumulation [8]. Measurements of oxalate in bony tissue from the iliac crest may be indicated to assess the presence and extent of calcium oxalate deposits in patients on any renal replacement procedure [9].

Table 1 lists the relevant chemistries in two cases, with pyridoxine-responsive and pyridoxine-resistant PH1, respectively. It is shown that, off pyridoxine and at equal levels of glomerular filtration rate (GFR), both patients have a clear-cut increase in oxalate and glycolate levels, which, however, are higher in pyridoxine-resistant PH1. Correspondingly, while no AGT activity occurs in the latter, a residual activity and a significant in vitro activation is detected in the pyridoxine-responsive case. Glycolate and oxalate levels decline significantly upon pyridoxine supplementation in one, whereas virtually no response is seen in the other.

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Current therapeutic concepts

In a recent nationwide survey of PH1 in Switzerland, Kopp and Leumann found that 22.7% of patients were pyridoxine sensitive [10]. The recognized heterogeneity of PH1 requires that clear-cut differentiation among the several forms of the disease be pursued. Specifically, assessment of residual AGT activity and possibly associated pyridoxine responsiveness have important implications for the management of the disease at any stage. Milliner et al. have reported that long-term combined treatment of PH1 with orthophosphate and pyridoxine preserved renal function over a 10 year follow-up [11]. Allen et al. have described a patient with PH1 with clinical and biochemical evidence of pyridoxine responsiveness who had an excellent renal function and no stone recurrence 1 year after live-related renal transplantation [12].

It emerges that response to pyridoxine may crucially influence the outlook for patients with different forms of PH1. Reportedly, renal function declines progressively to ESRF in patients who do not respond, they must be started on dialysis therapy early and often respond very poorly after isolated kidney graft, due to rapid recurrence of renal and systemic oxalosis. On the contrary, pyridoxine responsive patients often have stable decreases in plasma and urine oxalate and renal function maintains for a long time. In such patients who progress to ESRF, possibly because PH1 and pyridoxine responsiveness have been overlooked, isolated kidney grafts often have a favourable outcome, provided they are given pyridoxine therapy. The behaviour of one patient of ours with the pyridoxine-responsive form confirms the above contention. Diagnosis of PH1 and pyridoxine responsiveness were established only after she had developed ESRF and had been subjected to isolated kidney transplantation. Renal function improved upon pyridoxine addition and was still satisfactory 42 months thereafter. Pyridoxine produced profiles of oxalate and glycolate very similar to those seen after combined hepatorenal transplantation in one other patient with the pyridoxine-resistant variant (Figure 1). Glycolate levels normalized in both patients indicating that de novo synthesis of oxalate had reverted to normal by pyridoxine and by the grafted liver, respectively. Plasma and urine oxalate excretion decreased initially in both cases, but did not normalize, levelling off at 2–3 mmol/24 h. This sustained hyperoxaluria was due to progressive wash-out of oxalotic deposits favoured by a stable undersaturation of body fluids with calcium oxalate. This phenomenon hitherto was known to occur in patients subjected to combined hepatorenal transplantation [13], but actually occurred also in our pyridoxine-treated kidney-grafted patient. This contention was also supported by the results of serial bone biopsies which showed a significant decrease in oxalate in bony tissue.

Conclusions and recommendations

Some points can now be made concerning the policy to be adopted in patients with PH. First, patients with PH should be classified according to genetic variant, i.e. type 1 or type 2. Second, those with hyperglycolic aciduria should be categorized further with respect to pyridoxine responsiveness. They are likely to belong to this subset if they exhibit residual AGT activity on liver biopsy and decreased de novo glycolate synthesis upon pyridoxine administration. We contend that response to pyridoxine can be detected by glycolate measurements at any stage of the disease, using methods suitable for plasma, urine and dialysis fluids. Third, in the setting of systemic oxalosis, measurements of oxalate variations upon pyridoxine supplementation may give misleading results, since the potential decrease in oxalate biosynthesis can be masked by a concurrent increase in oxalate dissolution from tissue deposits. Fourth, long-standing hyperoxaluria after successful transplantation requires careful monitoring and prevention of calcium oxalate stones until normalization of oxalate excretion. Serial measurements of bony content of oxalate may be helpful to estimate the residual burden of oxalate deposits. Fifth, because up to 20–30% of patients with PH1 are expected to be
Fig. 1. Profiles of relevant plasma and urine chemistries and calcium oxalate saturation levels before and over 42 month follow-up on pyridoxine supplementation in a patient with pyridoxine-responsive PH1 with isolated kidney transplantation (left panel). The same parameters before and over 12 month follow-up after hepatorenal transplantation in a patient with pyridoxine-resistant PH1 (right panel).

Pyridoxine-responsive

Pyridoxine-resistant

References