Letter and Reply

The patient with acute renal failure and non-dilated urinary tract

Sir,

We read with great interest the recent teaching point by Canavese and colleagues [1]. As they mention, certain conditions are more likely to result in non-dilated obstructed nephropathy [2]. Certainly in this case, from the clinical history of carcinoma and sudden anuria and previous CT scan result, a high index of suspicion about tumour involving the periurethral tissue or urethral wall, producing a functional rather than an anatomical obstruction was apparent. We have previously reported a case of bilateral non-dilated obstruction due to ureteric calculi which was suspected on the clinical history and identified only after helical computerized tomography [3]. Although ultrasound may be considered the ‘gold standard’ test for the diagnosis of obstructive nephropathy, computerized tomography may be more fruitful in discovering the aetiology of obstruction. In their case, as in ours, the clinical history and not the ultrasound should guide ones diagnosis.

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Reply

We thank Dr Bhandari very much for his comment, which underscores the fact that the evidence of an obstructive non-dilated acute renal failure has to be kept in mind in the day-to-day clinical practice. It is known that helical computer tomography may offer more sophisticated information in comparison with traditional computed tomography.

We agree that attempts may be made to look for further information provided by helical CT in cases of patients with high suspicion for obstruction mainly by improving evidence of abnormalities of the urinary tract eventually leading to obstruction.

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Letters

Nephrotic syndrome associated with recombinant hepatitis B vaccination: a causal relationship or just a mere association?

Sir,

Recombinant hepatitis B vaccine has been shown to be effective in preventing both the spread of hepatitis B virus infection and its complications of healthy children and adults. Side-effects of this highly immunogenic vaccine are generally minor, although a few of major side-effects such as erythema nodosum, uveitis, polyneuropathy, acute myelitis and acute glomerulonephritis have been reported [1]. So far there is only one reported adult case presenting with minimal-change nephrotic syndrome (MCNS) after hepatitis B vaccination [2].

We report the first childhood case presenting with nephrotic syndrome after the second inoculation of recombinant hepatitis B vaccine.

Case

A 3-year-old boy presented with a 4-day history of swelling of the eyelids 17 days after the second inoculation of recombinant hepatitis B vaccine. There was no history of drug ingestion, allergy, or an upper respiratory tract infection. The past and family medical histories were unremarkable. On physical examination, blood pressure was 90/60 mmHg, he was at the 75th percentile for weight and at the 50th percentile for height. Generalized oedema was present.

Laboratory studies disclosed the following values: haemoglobin 13.2 g/dl, white blood cell count 9800/mm³, blood urea nitrogen (BUN) 12 mg/dl, creatinine 0.5 mg/dl, total protein 5.7 g/dl (normal range 6–8 g/dl), albumin 2.9 g/dl (normal range 3.5–5 g/dl), cholesterol 526 mg/dl (normal range 120–220 mg/dl), triglyceride 200 mg/dl (normal range 80–120 mg/dl). Electrolytes, calcium, phosphorus, and third component of the complement were all normal. Urinalysis revealed a specific gravity of 1022 with severe proteinuria, and microscopy showed 2–3 leukocytes and granular casts per high-power field. Urinary protein loss was 1.6 g/kg/day. Hepatitis B antigen was negative, anti-HBs antibody was 123 IU/ml. Serological studies for hepatitis C, Ebstein–Barr virus and cytomegalovirus were all negative. Kidney biopsy was not performed, since the patient was 3 years old; his blood pressure was normal and haematuria was not present. Following 20 days of corticosteroid therapy (2 mg/kg/day, p.o.) a complete remission was observed and he was diagnosed as MCNS.

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The pathophysiology of MCNS is still unknown. Although it has been proposed that immune-related mechanisms are involved, there has been little proof for an antibody-mediated aetiology. Viral upper respiratory tract infections are well recognized triggers of the disease onset and of relapses, suggesting the presence of immune mechanisms. Furthermore, non-complement fixing complexes have been detected in patients with MCNS [3]. We have previously demonstrated the presence of T-cell subset changes and high interleukin-2 receptor expression on peripheral lymphocytes of the patients in relapse, suggesting that T-cell activation may be involved in the immunopathogenesis [4].

Recombinant hepatitis B vaccine that is highly immunogenic, has been used world-wide. Arakawa et al. [5], had observed that there was no significant correlation between the strength of the hepatitis B virus antibody response and the lymphocyte subsets in the peripheral blood after vaccination, although low OKT4+/OKT8+ cell ratios tended to be increased in the non-responders.

We report the second patient with MCNS associated with recombinant hepatitis B vaccine in the medical literature. The subject of the vaccine–MCNS relationship needs to be clarified, considering the supports about the pathophysiology of MCNS. Since hepatitis B vaccination is important for the prevention of the spread of hepatitis B infection, it is clear that the risk–benefit ratio leans towards the advantages of disease prevention. On the other hand, frequency of the complications should be more accurately determined in order to evaluate a causal relationship between the hepatitis B vaccine and nephrotic syndrome.

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Nephrotic syndrome secondary to primary immunoglobulin-G mesangioproliferative glomerulonephritis

Sir,

Mesangioproliferative glomerulonephritis [1] is the most prevalent form of glomerular disease. Several immunoglobulin deposition patterns have been described by immunofluorescence microscopy in mesangioproliferative glomerulonephritis; IgA is the most commonly found but IgM, C3, and C1q have also been reported. To the best of our knowledge, there has been no report of isolated IgG mesangioproliferative glomerulonephritis as a specific disease entity outside of systemic lupus erythematosus in the adult population.

Case

A previously healthy 48-year-old gym teacher presented in May of 1994 with acute onset of generalized oedema. He had no history of unusual environmental or occupational exposure and denied use of the counter or recreational drugs. Initial laboratory investigations revealed a normal serum creatinine (82 μmol/l) and urea (5.7 μmol/l). Serum albumin and total protein were low at 25 g/l (38–50 g/l) and 48 g/l (62–78 g/l), serum cholesterol was high at 7.93 mmol/l and had nephrotic range proteinuria (3.9 g) on 24-h urine collection. Serum protein electrophoresis and immunoelectrophoresis did not reveal any monoclonal peaks. Complements C3 and C4, anti-nuclear antibody (ANA) and anti-deoxyribonucleic acid (anti-DNA) were all negative. Hepatitis B and C serology were negative. Kidneys were normal size on ultrasound and biopsy revealed IgG mesangioproliferative glomerulonephritis.

The patient initially received prednisone 160 mg every second day (1.6 mg/kg) for 8 weeks. As there was no response, a second 8-week course of steroid treatment was prescribed. On steroid treatment his renal function remained stable but nephrotic syndrome persisted and he had repeated episodes of cellulitis requiring antibiotic treatment. Cyclophosphamide 150 mg daily (1.5 mg/kg) was added and continued for 8 weeks. Because of lack of response at the end of this period, cyclophosphamide was discontinued and steroids were tapered to discontinuation over the following 2 months.

One year later he continues to have nephrotic syndrome with normal renal function without any significant response to the above regimen. He remains on an ACE inhibitor to reduce proteinuria, an HMG-CoA reductase inhibitor to treat hypercholesterolaemia, and a loop diuretic to control oedema.

On light microscopy there were 17 glomeruli that were slightly enlarged and showed focal mesangial expansion and mild hypercellularity. Small scattered areas of interstitial fibrosis with a few entrapped atrophic tubules were present. The blood vessels were unremarkable. Immunofluorescence revealed granular deposits of IgG and C3 along the capillary basement membranes and mesangial areas. On electron microscopy small electron dense deposits were noted in mesangial locations along with effacement of epithelial foot processes.

Comment

Mesangioproliferative glomerulonephritis is an entity which is defined by its light microscopy features. However, because of the non-specificity of the character and distribution of the proliferative lesion by light microscopy alone, patients with resolving PSGN, and systemic diseases (SLE, HSP), may also fit into this category [2]. Although IgA nephropathy, the most common cause of glomerulonephritis [1] falls in this category, it is not the only one and other subtypes such as IgM, C3q and C1q have also been described. There is little published information about primary glomerulopathies associated with mesangial IgG deposits and only reported in the paediatric population [3,4].

The pathognomonic finding in IgA nephropathy is by immunofluorescence microscopy which demonstrates prominent granular deposits of IgA as well as some IgG and C3 [1]. Patients with this disorder typically present in one of several ways. They may have either recurrent episodes of gross haematuria, usually following a respiratory tract infection, microscopic...
haematuria and mild proteinuria, or may present with nephrotic syndrome. Rarely they may also present with an acute glomerulonephritis picture characterized by oedema, hypertension, haematuria and renal insufficiency.

IgM and C1q nephropathy may represent variants of minimal change disease but some believe they represent distinct conditions. IgM and C1q nephropathy frequently present with haematuria, asymptomatic proteinuria or nephrotic syndrome. IgM nephropathy is characterized by predominately mesangial deposits of IgM and complement [5], while in C1q nephropathy there are predominately C1q deposits with mild deposition of IgG, IgA and IgM [6]. Our patient had no IgA or IgM mesangial deposits and only small amounts of C3, C4 and C1q and would therefore not belong in any of the above categories.

IgG deposits have been noted in patients with lupus nephritis [7]. Lupus can be distinguished from IgA nephropathy based on a more predominant deposition of IgG versus IgA as well as substantial C1q deposition [8]. Our patient had no evidence of IgA and only minimal amounts of C1q. This patient demonstrated no clinical symptoms of SLE. His ANA and anti-DNA were both negative and the complement levels were normal.

In a review by Germuth et al., they reported 12 children with asymptomatic proteinuria or recurrent haematuria who had small deposits throughout the mesangium which stained for IgG and C3 [4]. Yoshikawa et al. presented 10 children who had IgG-associated diffuse mesangial proliferative glomerulonephritis [3]. On immunofluorescence, all cases demonstrated diffuse, global predominantly mesangial IgG deposits. In most cases, C3 was identified, and in three patients, C1q. These findings are similar to those noted in our patient with IgG and C1q deposits along the glomerular basement membrane and mesangial regions. In both series, the children were given a good ultimate prognosis, however, it was noted in Yoshikawa’s study that some of the children had a poor initial response to treatment with prednisone (4 out of 10 children were steroid resistant early on). At the latest follow up, renal function was noted to be normal in all patients with six achieving clinical remission and four continuing to have slight haematuria and/or proteinuria. Unfortunately in our case, we have been unable to achieve remission despite treatment with cyclophosphamide and prednisone and his peripheral oedema, hyperlipidaemia and hypertension remained problematic.

This case suggests that IgG mesangio proliferative glomerulonephritis is a distinct immunopathological entity which is not restricted to the paediatric population. Caution should be made that only a single biopsy was done on this patient, and therefore, we do not know whether additional deposits occur at a future time in the natural history of this disease. The findings of a distinct IgG nephropathy supports earlier work by Yoshikawa and Germuth who similarly found IgG mesangial deposits in children. To date, we have not discovered an optimal treatment plan for this patient and unlike the children in whom they feel the overall prognosis is favourable, outcome remains less clear in this case.

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Cryoglobulinaemia, membranoproliferative glomerulonephritis and pANCA in a patient treated with carbamazepine

SIR,

Recently in this journal Lamprecht et al. described two patients with type II cryoglobulinaemia, cANCA and immune complex glomerulonephritis [1], and Messiaen et al. reported a patient with subacute bacterial endocarditis, type III cryoglobulinaemia, necrotizing glomerulonephritis and pANCA [2]. We observed a similar patient, who was treated with the antiepileptic drug carbamazepine and developed type III cryoglobulinaemia with membrano proliferative glomerulonephritis and anti-myeloperoxidase antibodies.

Case

The 40-year-old man had received the drug from the age of 8 years. Ten years ago a carbamazepine-induced autoimmune syndrome had been suspected. The patient suffered from a lupus-like illness with hypocomplementaemia, pancytopenia and splenomegaly. A type III cryoglobulin, anti-DNA antibodies, anti-dsDNA antibodies, cold agglutinins, anti-Ro and anti-La antibodies were detected. A splenectomy was performed, but carbamazepine was not discontinued. Ten years later the patient was admitted because of an elevated serum creatinine of 250 μmol/l, heavy proteinuria and a nephritic urinary sediment. He complained of migrating arthralgias. Complement C3 (0.22 g/l) and C4 (0.7 g/l) were markedly reduced. A type III cryoglobulin was still present. Tests for ANA (1:640), anti-dsDNA antibodies (1:10) and pANCA (1:1280) were positive. The pANCA was confirmed by myeloperoxidase-specific ELISA. A renal biopsy showed membranoproliferative glomerulonephritis type I with cellular crescents in two out of 10 glomeruli. Subendothelial granular deposits of IgG, IgM, C1q, C3 and terminal complement complex were detected by immunofluorescence. Tests for anti-HCV antibodies and HCV-RNA were negative. Echocardiography did not show any signs of endocarditis. Carbamazepine was discontinued. Because of progressive renal failure immunosuppressive therapy with prednisolone and plasma exchange was initiated. Due to severe pneumonia treatment had to be stopped. Four months later the patient

Case

The patient was referred to our renal clinic in March 1996 because of persistent proteinuria (∼ 1 g/24 h) with granular casts and microhaematuria, both lasting since at least 1 year, and a very recent history (a few days) of migratory arthritis involving both hands and wrists. His past history included patchy alopecia 3 years previously and three febrile episodes without any symptoms or signs in 1995. At that time, a chest roentgenogram showed right fibrinous pleurisy. He was treated by means of broad-spectrum antibiotics. At admission, he had no hypertension; his renal and liver function tests and blood cell counts were normal; the erythrocyte sedimentation rate was 116 mm h; serum IgG levels were slightly elevated at 16.9 g/l (normal range 8.0–15.0); serum IgM, IgA, C3 and C4 levels were normal. The ANA titre was 1:640, anti-nDNA levels were > 300 IU/ml (negative when < 30); other serologies included positivity for both RNP and Sm antibodies, and negativity for both La and Ro antibodies. Taken together, these clinical and laboratory data allowed the diagnosis of SLE [6].

Furthermore, thyroid tests showed low levels of FT3 and FT4 (1.9 and 4.9 pg/ml, respectively; normal ranges 2.5–5.6 and 6.0–16.0, respectively), high levels of serum TSH (47.7 μU/ml, normal range 0.3–4.0) and high titres of antithyroglobulin and anti-microsomal antibodies (>5000 and 3000 U/ml, respectively; negative when <100 and 50, respectively). Echography showed an enlarged thyroid gland with small areas of focal hyperplasia. Taken together, these laboratory data allowed the diagnosis of Hashimoto’s disease.

Finally, a percutaneous renal biopsy was performed: glomerular histology showed intact tufts architecture and modest segmental mesangial hypercellularity. There was an absence of sclerosis and tubular atrophy. Immunofluorescence microscopy revealed distinct mesangial IgA and C3 with absence of IgG, IgM, IgC1q, C4 and fibrinogen. Electron microscopy confirmed the presence of electron-dense deposits confined to and throughout the mesangium and the absence of dense depositions in the capillary basement membrane. None of the mesangial electron-dense deposits showed the organized ‘fingerprint’ patterns seen in many typical cases of lupus nephritis. The myxovirus-like tubuloreticular inclusions sometimes described in endothelial cells of SLE patients were not identified. Renal biopsy then established the diagnosis of IgA nephropathy.

In summary, this 25-year-old male patient was affected by IgA nephropathy, SLE and Hashimoto’s disease. He started a treatment consisting of prednisone (1 mg/kg per day for 4 weeks) and levothyroxine (50 μg per day). Clinical symptoms rapidly abated; at the present follow-up time point (18 months), he continues to be treated with prednisone (10 mg per day) and levothyroxine (50 μg per day); his renal function is very good, proteinuria of 1 g/24 h and microhaematuria still persist, ANA and anti-nDNA titers are undetectable, leukopenia (3.0 × 10⁹ white cells/l) appeared.

Discussion

The propositus has rather characteristic clinical and laboratory features for the diagnosis of SLE, even excluding renal involvement [6]. The first point to be stressed is that the patient is male: as is well known, SLE is predominantly a
The renal symptoms of the propositus were not discriminative between lupus nephritis and IgA nephropathy; however, the histological diagnosis of IgA nephropathy was straightforward in that glomerular lesions consisted almost exclusively of mesangial IgA and C3 immune depositions, with modest hypercellularity and sclerosis [1]. Such an observation is unexpected in a patient with SLE. One may argue that the predominant mesangial IgA immune complex is a morphological subtype of lupus nephritis; however, the absence of other immunoglobulins, in particular of IgG, and of complement C1q or C4 of the classical pathway are not the usual diagnostic criteria. Without the clinical history, the histological diagnosis of lupus nephritis would have not been considered, and even with established clinical SLE, the histological findings do not justify a diagnosis of lupus nephritis or of an atypical form [5].

Occurrence of a non-lupus nephritis in patients with SLE is a rare event and of pathogenic interest [2–5]. The pathogenesis in lupus nephritis remains incompletely understood; both experimental and human observations indicate that several effector mechanisms of immune regulation are altered. No specific aetiology can be identified, but lupus nephritis is regarded as the prototype of chronic immune complex glomerulonephritis [8].

The pathogenesis of IgA nephropathy is also uncertain and its aetiology is unknown [9]. Although both lupus nephritis and IgA nephropathy are immune complex-mediated diseases, the pathogenesis of each appears different even though much remains undetermined. Their relatively distinct clinical and histological features, including their contrasting allograft recurrence, seem to support such a notion [9–11]. Although SLE is clearly an autoimmune disease, attempts to relate IgA nephropathy to autoimmunity are contradicting but confirm a lack of significant autoantibodies in IgA nephropathy [12].

In conclusion, the propositus may represent a subset of SLE with uncertain host factors or immune response resistant to the expression of lupus nephritis. In fact, the 18 month follow-up confirms a rather indolent renal disease, compatible with the diagnosis of IgA nephropathy, and also suggests that factors preventing the development of lupus nephritis in this patient are maintained [5].

**Acute tubulo-interstitial nephritis and uveitis syndrome (TINU syndrome). Occurrence of uveitis after stopping steroids**

Sir,

Acute interstitial nephritis with concomitant uveitis (TINU syndrome) is a rare condition involving mostly adolescent females [1]. About fifty cases are described in the literature since the first report about 20 years ago [2–4] Uveitis, which tends towards relapses usually follows interstitial nephritis by only few weeks to 8 months [4,5]. We report a young female patient with acute interstitial nephritis and marked decrease of renal function, who developed acute anterior uveitis after withdrawal of oral steroid medication.

**Case**

A 14-year-old girl was admitted to another hospital with a 3-week history of intermittent bilateral flank pain, fatigue, nausea and a weight loss of 8.5 kg in 3 weeks. Ten days before admission she suffered from an upper respiratory infection, which was treated with aspirin.

On admission she had fever up to 38.6°C. ESR was 120 mm/h, haemoglobin measured 81 g/l, haematocrit 0.27, platelet count 463 g/l, creatinine 2.4 mg/dl with a creatinine clearance of 50 ml/min/1.73 m². Serum urea was in normal range (34 mg/dl). Urine analysis revealed 8–10 leukocytes in the sediment with a proteinuria of tubular origin ranging between 0.3 and 0.5 g/24 h.

Renal ultrasound showed slightly enlarged kidneys without any abnormalities. Bone marrow aspiration revealed eosinophils, an increase of plasma cells and megakaryocytosis. Non-caseous epitheloid-cell granulomas could not be detected. The patient was discharged from hospital with a medication of penicillin. Two weeks later the patient was referred to the Department of Internal Medicine of our hospital for further investigation. Laboratory findings at that time were as follows: ESR 81/127 mm/h, haemoglobin 87 g/l, haematocrit 0.27, platelet count 463 g/l, creatinine 2.4 mg/dl, creatinine clearance 27 ml/min/1.73 m². Urine analysis showed (normo-
Fatigue, nausea, weight loss and fever are often present and of the HLA system. characterized by a stereotypic, albeit non-specific course. TINU syndrome, with an additional pathogenetic importance preceding the nephritis by about 1 month, are frequently mechanisms, especially cell-mediated in the occurrence of

The first clinical symptoms of TINU syndrome, usually cases. These results confirm the pivotal role of immunological

Comments

The first clinical symptoms of TINU syndrome, usually preceding the nephritis by about 1 month, are frequently characterized by a stereotypic, albeit non-specific course. Fatigue, nausea, weight loss and fever are often present and may persist for several months. The inflammatory syndrome consists of a markedly increased erythrocyte sedimentation rate, high levels of C reactive protein and fibrinogen accompanied by a hyperproteinemia and sustained anaemia. Non-necrotic renal failure with signs of tubular dysfunction (proteinuria of tubular origin, renal glycosuria and generalized aminoaciduria) is always completely reversible and followed by an acute uveitis, which tends towards relapses. This time-sequence is typical for TINU syndrome. However, the development of uveitis immediately after withdrawal of a 5-month corticosteroid therapy for the tubulo-interstitial nephritis, necessitating systemic and topical steroids for another 20 weeks, has rarely been observed.

In general, the outcome of TINU syndrome is favourable: renal function normalizes spontaneously or after corticosteroid therapy [3,4,6]. However, in a review of the literature, Cacoub et al. [6] described two patients with deterioration of renal function who were not treated with corticosteroids.

The aetiology and the pathogenesis of TINU syndrome is still unknown. A possible aetiologic role of chlamydia infection, an antineutrophil cytoplasmic antibody was found [8]. However, the pathogenetic importance of the ANCA in this disease remains unclear.

In a recent blood cell immunological and serum analysis of a young boy with TINU syndrome, cytotoxic T-cell, macrophage and granulocyte activation was reported, which declined as the clinical symptoms improved. These findings provide evidence in favour of a significant role of this cell activation in the pathogenesis of the syndrome or as a part of a microbial-triggered immune response [9]. In addition Iitsuka et al. [5] observed numerous CD4-, CD8- and CD11c-positive cells in the interstitium of renal biopsy specimen of four patients with TINU syndrome. The tissue typing for HLA-A, B, C and DR antigens revealed identical HLA-CW3 in three patients and identical HLA-A24 in all four cases. These results confirm the pivotal role of immunological mechanisms, especially cell-mediated in the occurrence of TINU syndrome, with an additional pathogenetic importance of the HLA system.

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![Fig. 1. Clinical course (the relationship between renal function, therapy and the occurrence of uveitis) of a patient with acute tubulo-interstitial nephritis with uveitis (TINU syndrome).](image-url)
Successful treatment of anaemia of nephrotic syndrome with recombinant human erythropoietin

Sir,

The relationship between anaemia of the nephrotic syndrome (NS) and erythropoietin (Epo) deficiency has been recently reported and ascribed to loss of important amounts of Epo through urine [1]. Anaemia in NS has recently been treated successfully with rHuEpo [2–4]. However, as far as we know, no patient with anaemia, Epo deficiency, and urinary Epo losses treated with rHuEpo has been described.

We observed two patients suffering from severe anaemia, nephrotic syndrome, low plasma levels of Epo, and urinary Epo losses who had a good response to treatment with rHuEpo.

Case 1

A 65-year-old female with a clinical history of pluricom-plicated diabetes mellitus for 20 years and increased blood pressure (BP) was admitted to the hospital because cephalic instability and severe asthenia. A routine blood test detected increased ESR and normocytic normochromic anaemia. Physical examination showed a swollen facies with severe mucocutaneous pallor, BP 120/90, and hepatomegaly. Laboratory results showed haemoglobin 79 g/l, mean corpuscular volume 104.6 fl, mean corpuscular haemoglobin 32.5 pg, mean corpuscular haemoglobin concentration 311 g/l, ferritin 521 µg/l, transferrin 1.44 g/l, reticulocytes 64.4 × 10⁹/l, haptoglobin 0 g/l, folic acid 2.4 mg/ml, vitamin B₁₂ 1256 pg/ml, leucocytes 8.5 × 10⁸/l with normal formula, platelets 0.04 × 10¹²/l, fibrinogen 707 mg/100 ml, glucose 8.5 mmol/l, blood urea 15 mmol/l, plasma creatinine 151 µmol/l, total proteins 52.8 g/l, albumin 25.2 g/l, cholesterol 7.7 mmol/l.

Other biochemical parameters were normal. The immunological study (antineutrophil cytoplasmic antibodies (ANCA), antimuclear antibodies (ANA), complement levels, rheumatoid factor, and serum immunoglobulins) was negative. Tumoral markers (CEA, alpha-fetoprotein, CA-15.3, CA-125) were normal. Twenty-four-hour proteinuria was 201 g/l with normal albumin/creatinine ratio 5.7 g. Urinary sediment was normal. Isotopic glomerular filtration rate was 44 ml/min. Chest and abdominal X-rays, abdominal ultrasound, isotopic bone scan, fiberoptic gastroscopy, and rectocolonoscopy were normal. Bone marrow study showed increased iron stores but no sideroblasts, suggesting anaemia secondary to chronic process. Epo concentration in blood was 7.87 mU/ml (predicted Epo 76 mU/ml) and Epo in concentrated urine (>10) was 21.75 mU/ml. Treatment with enalapril was stopped and subcutaneous rHuEpo at a dose of 6000 U started twice a week. After 4 weeks, an increase of haemoglobin to 120 g/l and no changes in the 24-h urinary proteinuria were observed, and the patient showed a remarkable clinical improvement.

Case 2

A 67-year-old female with clinical history of rhinitis, occa-sional extrinsic conjunctivitis, long evolution hypertension treated with three drugs (β-blockers, doxazosin, and diuretics), C-virus-positive hepatopathy, and purpuric lesions on lower extremities was admitted to the hospital for nephrotic syndrome and mixed cryoglobulinaemia with renal involve-ment. She presented an anaemia of 2 months evolution, mild deterioration of renal function, and proteinuria. Physical examination showed good general condition, BP 190/95, severe oedema with fovea and purpuric lesions with scabs on lower legs. Blood tests showed haemoglobin 78 g/l, mean corpuscular volume 81.4 fl, mean corpuscular haemoglobin 26.2 pg, serum iron 32.4 mg/dl, ferritin 751 µg/l, transferrin 1.49 g/l, reticulocytes 85 550/mm³, haptoglobin 1.54 g/l, leucocytes 12.6 × 10⁹/l with normal formula, platelets 0.26 × 10¹²/l, fibrinogen 504 mg/100 ml, glucose 5.3 mmol/l, blood urea 7.2 mmol/l, plasma creatinine 148 µmol/l, total proteins 46.1 g/l, albumin 25.5 g/l, cholesterol 3.7 mmol/l, uric acid 536 mmol/l. The immunological study showed C3 60 mg/dl (normal 52–120), C4 6 mg/dl (normal 18–49), Ig A 56 mg/dl (normal 88–410); ANA and ANCA were nega-tive. C reactive protein was 50 (normal <6), rheumatoid factor 165 (normal <40), and no circulating immune complexes were detected. Hepatitis B antigen and antibodies, and human immunodeficiency virus antibodies were negative. Hepatitis C virus antibodies (immunoblot) and C virus RNA (PCR) were positive. IgG polyclonal cryoglobulins were positive. Twenty-four-hour proteinuria was 10.5 g. Urine analysis showed 50–60 erythrocytes/HPF (20% RBC casts). Serum Epo was 10 mU/ml (predicted Epo 120) and urinary Epo was 8.12 mU/ml. Chest X-ray showed severe cardiome-galy and left pleural effusion. The echocardiogram showed pericardial effusion. Abdominal ultrasound scan showed mild hepatosplenomegaly, and the kidneys had normal echo-structure and size. Renal biopsy revealed a type I mesangio-capillary glomerulonephritis and intraluminal deposits which stained strongly with eosin and PAS, suggesting a cryoglobulin-inaemic glomerulonephritis. Treatment with rHuEpo was started, at a dosage of 4000 U three times a week. Four weeks later the anaemia improved, reaching a haemoglobin of 109 g/l and 24-h proteinuria was 8.3 g.

Comments

The NS is the clinical consequence of an increase in glomerular permeability that is produced by a lesion of the glomerular filtration barrier. The loss of proteins is related to their size, shape, and electrical charge. Epo is a 30.4-kDa glycoprotein produced in the liver in the fetus and in the kidney in adults, with a molecular weight less than albumin. Thus it can be lost in the urine in patients with the NS.

Animal and human experimental studies have related the NS anaemia to Epo deficiency [1]. In some cases this has been ascribed to loss of large quantities of Epo in urine [1], but many patients with NS, often much more severe than in two cases herein described do not develop anaemia. In anemic patients additional factors may contribute to the development of anaemia, such as decreased Epo production (known to be produced in the peritubular-interstitial cells), increased Epo degradation [5] (the liver is the main site of the degradation), or the presence of associated disease (dia-betes, vasculitis etc.), or deficiency of iron, folate, cobalamin, zinc, or copper, and finally administration of drugs, e.g. ACE inhibitors potentially interfere with synthesis of or response to Epo. In the two cases reported, important loss of Epo in the urine was detected as the cause of the low plasma Epo. Treatment with rHuEpo was successful in both of our patients. After 8 weeks of therapy clear clinical improvement accompanied by a substantial increase in haemoglobin concentration were noted; no changes in 24-h urinary protein excretion rates were observed. Hypertension was not observed, and renal function remained unchanged.

In conclusion, anaemia in patients with NS may be related
Neurological complication during imipenem/cilastatin therapy in uraemic patients

SIR,

A 79-year-old man treated with CAPD since 1993 was admitted to our unit with abdominal pain and fever. Laboratory studies showed serum creatinine 10.2 mg/dl, urea 96 mg/dl, sodium 141 mEq/l, potassium 4.0 mEq/l, glucose 113 mg/dl. His body weight was 69 kg. Peritoneal dialysate was turbid with leucocyte count of 50/hpf predominantly neutrophils and Gram-negative bacteria were isolated. His peripheral leucocyte count was 10900/mm³. A diagnosis of peritonitis was made and treatment with intravenous imipenem/cilastatin (I/C) 500 mg every 12 h was started. Three days later, the patient experienced flapping tremor and an absence lasting for ~1 min followed by a prolonged period of mental confusion and confabulation. The computerized axial tomography of the brain as well as the electroencephalogram were unremarkable. Therapy with haloperidol and promazine was started while I/C was discontinued and substituted with vancomycin. The patient recovered both from peritonitis and mental confusion within one week and was discharged 15 days later. At present he is well at home.

Imipenem, a beta-lactam agent, is the first carbapenem antibiotic used in clinical practice. It is filtered at the glomerulus and hydrolyzed in the brush border. Imipenem is given as a one to one combination with cilastatin, an inhibitor of the brush border dehydropeptidase, to prevent enzymatic degradation that would compromise efficacy in the urinary tract. The combination I/C has broad-spectrum antibacterial properties. It is effective against Gram-positive species including enterococci and Gram-negative species including pseudomonas [1].

Adverse events of I/C have been predominantly related to the gastrointestinal system (nausea and vomiting) or to the skin (rash) but neurological complications, including convulsion, extrapyramidal symptoms and seizures have also been reported [2]. The frequency of these complications is generally low and is dose-dependent. The principal risk factors for developing neurological complication are central nervous system abnormalities, excessive dosage, and renal impairment [3].

In patients with normal renal function a dose of 500 mg every 6 h to be doubled in seriously infected patients was discharged 15 days later. At present he is well at home. A 79-year-old man treated with CAPD since 1993 was admitted to our unit with abdominal pain and fever. Laboratory studies showed serum creatinine 10.2 mg/dl, urea 96 mg/dl, sodium 141 mEq/l, potassium 4.0 mEq/l, glucose 113 mg/dl. His body weight was 69 kg. Peritoneal dialysate was turbid with leucocyte count of 50/hpf predominantly neutrophils and Gram-negative bacteria were isolated. His peripheral leucocyte count was 10900/mm³. A diagnosis of peritonitis was made and treatment with intravenous imipenem/cilastatin (I/C) 500 mg every 12 h was started. Three days later, the patient experienced flapping tremor and an absence lasting for ~1 min followed by a prolonged period of mental confusion and confabulation. The computerized axial tomography of the brain as well as the electroencephalogram were unremarkable. Therapy with haloperidol and promazine was started while I/C was discontinued and substituted with vancomycin. The patient recovered both from peritonitis and mental confusion within one week and was discharged 15 days later. At present he is well at home.

Imipenem, a beta-lactam agent, is the first carbapenem antibiotic used in clinical practice. It is filtered at the glomerulus and hydrolyzed in the brush border. Imipenem is given as a one to one combination with cilastatin, an inhibitor of the brush border dehydropeptidase, to prevent enzymatic degradation that would compromise efficacy in the urinary tract. The combination I/C has broad-spectrum antibacterial properties. It is effective against Gram-positive species including enterococci and Gram-negative species including pseudomonas [1].

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In patients with normal renal function a dose of 500 mg every 6 h to be doubled in seriously infected patients has been recommended [4]. If the glomerular filtration rate (GFR) ranges between 10 and 30 ml/min/1.73 m² the daily dose should be reduced by 50% [5]. In patients with GFR <10 ml/min/1.73 m² or in dialysed patients the dose should be reduced to 500 mg every 12 h. With such a dosage no neurological side effect was reported in previous experiences [6]. Since haemodialysis results in the removal of 40–70% of imipenem and variable amount of cilastatin depending on the type of dialysis and the filter employed, it was also suggested that a supplemental dose may be administered at the end of the dialysis session [5]. There are no data on peritoneal dialysis. Some textbooks suggest an average dose of 500 mg every 12 h [7,8].

Reviewing our own experience, we found six patients treated with I/C who developed neurological complications (Table 1). Excluding the patient no. 3 who had a previous cerebral ischaemia, none of the others had additional risk factor. All of our patients recovered completely from neurological complications but three patients died a few days later because of the basic infection. In our patients the time interval between I/C administration and seizures ranged between a few hours and a few days. Therefore it is difficult to assess a time-related event. In all the patients the antibiotic dosage was appropriately adjusted according to the residual renal function. On the other hand, some uraemic patients developed neurological complications after 1–2 doses of I/C.
suggested that factors other than inappropriate dosage may be involved in the pathogenesis of I/C related neurotoxicity. In this setting, it is of relevance that the binding between imipenem and the gamma-aminobutyric acid receptors of the brain is stronger than with other beta-lactams [9]. This might explain at least in part why uraemic patients are particularly exposed to neurological complications. On the basis of our experience we feel that the dose of I/C usually suggested for uraemic patients may be excessive and should be reduced to one half.

In summary, it seems prudent that I/C is prescribed to uraemic patients only in the case of severe infections and/or when other antibiotics failed. The dose should not exceed 500 mg per day in dialysis patients. Finally, a careful monitoring of uraemic patients is recommended during I/C administration. In the presence of any neurological sign or symptom during I/C therapy, the antibiotic could be suspected as potentially responsible and should therefore be discontinued immediately in order to prevent severe complications.

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**Baclofen neurotoxicity in chronic haemodialysis patients with hiccup**

Sirs.

Baclofen, a centrally acting gamma-aminobutyric acid agonist is a commonly used pharmacotherapy for spasticity of spinal origin [1]. It has also been recommended for the initial treatment of intractable hiccups of several aetiologies [2]. Moreover, baclofen has been considered as one of the agents of choice in the treatment of intractable hiccups in patients with uraemia [3–6]. So far three reports of baclofen toxicity have been reported in patients with renal insufficiency [7–9].

We report here two haemodialysis patients with persistent hiccups who were treated with baclofen and developed baclofen-associated encephalopathy. The neurological picture resolved with discontinuation of the drug and early haemodialysis.

**Case 1**

A 69-year-old man treated by haemodialysis in another unit presented persistent hiccups during 7 days. Treatment with oral baclofen 5 mg/8 h receiving a cumulative dose of 20 mg in 36 h. The patient developed progressive confusion and coma, and was referred to our unit for evaluation. Haemodialysis had been initiated 19 months earlier for end-stage renal disease secondary to diabetic nephropathy. At admission to the hospital he had a Cheyne-Stokes respiration and grade 1 coma. Blood pressure was 150/90 mmHg, the temperature was 37°C. Except for coma, the neurological examination was normal. On the day pre-dialysis laboratory data showed haemoglobin 13.6 g/dl, WBC 8000/mm³ with normal differential count and platelets 213,000/mm³. Serum sodium was 136 mmol/l, potassium 3.8 mmol/l, bicarbonate 21 mmol/l, calcium 2.5 mmol/l, phosphate 1.5 mmol/l, urea 33 mmol/l, creatinine 1105 μmol/l, and glucose 13.8 mmol/l. The transaminases were normal. A lumbar puncture revealed normal pressure. The cerebrospinal fluid cells, albumin and glucose content were normal. A brain computerized tomography (CT) showed multiple calcifications and infarcts in the white matter, signs of cortical atrophy and attenuation in the white matter of the periventricular regions (leukoaraiosis). Baclofen-associated encephalopathy was considered to be the most likely explanation for the neurological picture. The drug was discontinued and immediate haemodialysis was performed. After the first 4-h haemodialysis session there was a rapid recovery of his level of consciousness, and on the second day after the second haemodialysis session, neurological recovery was complete. The patient was discharged from the hospital 4 days after admission in excellent condition. Afterward he remained well on haemodialysis, and to date the hiccups did not return.

**Case 2**

A 71-year-old man with end-stage renal disease secondary to diabetic nephropathy was treated by haemodialysis during 9 years in another unit. He presented with persistent hiccups during several days and was given oral baclofen 10 mg three times daily, receiving a cumulative dose of 120 mg in 4 days. The patient developed progressive muscle weakness, difficulty in walking and confusion, and was referred to our unit for evaluation. At admission to the hospital he was conscious but with drowsiness, his blood pressure was 120/80 mmHg, and his temperature was 37°C. The patient complained of diffuse abdominal pain. Except for generalized hypotonia, the neurological examination was unremarkable. Laboratory data showed haemoglobin 11.4 g/dl, WBC 6000/mm³ with normal differential count and platelets 210,000/mm³. Serum sodium was 143 mmol/l, potassium 5.5 mmol/l, bicarbonate 25 mmol/l, calcium 2.5 mmol/l, phosphate 2.3 mmol/l, urea 40 mmol/l, creatinine 698 μmol/l, and glucose 6.4 mmol/l. The transaminases were normal. An ultrasound exploration of the abdomen was unremarkable. A brain CT showed signs of cortical and subcortical atrophy, leukoaraiosis, and cortical infarcts in both occipital lobes. After discontinuing...
baclofen and renewed haemodialysis the neurological symptoms receded. As the hiccups persisted the patient was treated with metoclopramide 20 mg/day which was unsuccessful. Chlorpromazine was initiated at a dose of 30 mg/day and hiccups improved, although failed to resolve completely.

Comment

Baclofen is administered at 5–10 mg every 8 h, and the normal therapeutic serum is 80–400 ng/ml. It is primarily excreted by glomerular filtration with a clearance proportional to creatinine clearance. The half-life is between 4.5 and 6.8 h in healthy subjects, but it increases in end-stage renal disease [10]. Thus, baclofen accumulation and neurotoxicity may occur with normal doses in patients with impaired renal function [8,9]. Indeed in several countries renal failure is listed as a contraindication to the use of baclofen.

Although baclofen serum concentrations were not measured, in our patients the development of baclofen-related encephalopathy was obvious. Both patients received normal doses and short-term baclofen therapy, and the deep central nervous system depression noted in these patients is clearly explained by reduced clearance of baclofen [11,12]. They had arteriosclerotic cerebrovascular disease and pre-existing cerebral damage may have accentuated the development of toxicity in these patients.

In several cases of baclofen overdose haemodialysis and haemoperfusion were effective for removal of baclofen [8,9,13,14]. We found that after cessation of baclofen therapy when haemodialysis was instituted both patients showed progressive neurological improvement. The delay of several hours in recovery of consciousness after haemodialysis could be due to a delay in the clearance of baclofen from the central nervous system.

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11. Gerkin R, Curry SC, Vance MV, Sankowski PW, Meinhart RD.


Sporious hepatitis B surface antigen detection in a haemodialysis patient

Sir,

There is a risk of transmission of blood-borne infections in patients receiving maintenance haemodialysis and it is now Department of Health policy in the UK to recommend hepatitis B vaccination in all patients with progressive renal disease and dialysis unit staff to reduce the risk of hepatitis B infection. Complications are rare after vaccination and generally comprise allergic reactions. This case illustrates an unusual problem with important implications for the care of the dialysis patient.

A 35-year-old man with end-stage renal failure secondary to adult polycystic kidney disease commenced chronic haemodialysis in August 1996. He was accepted onto the renal transplantation programme after bilateral nephrectomy to allow easier surgical access. Routine 3-monthly blood tests for hepatitis B surface antigen (HBsAg), hepatitis C virus antibody, and human immuno-deﬁciency virus antibody were persistently negative. After 6 months he was admitted late one Saturday evening to the tertiary centre for renal transplantation. Unfortunately urgent HBsAg screening was positive by the screening enzyme immunoassay (EIA) (VIDAS, Biomerieux, France) with a test value of 0.18 against the cut-off value of 0.13. Thus renal transplantation was not possible since there was a danger that the patient was in an early phase of hepatitis B infection. The following day he was haemodialysed in the host institution but in an isolation facility rather than the chronic dialysis facility. The patient was interviewed and admitted no risk factors for hepatitis although he had had a blood transfusion at the time of nephrectomy. Urgent liver function tests were normal and repeat HBsAg was positive using the same and a different (Abbott, USA) EIA kit. He then admitted that 6 days earlier he had received the first dose of hepatitis B vaccine (Engerix B, SmithKline Beecham, UK) from his primary care physician. Further in vitro testing was performed to investigate the problem. Two reactions were set up, one with 150 μl of patients serum with 10 μl of hyperimmune anti-HBs serum and a control using patients serum and 10 μl of normal anti-HBs negative serum. The HBsAg EIA assay was then repeated after 10 min incubation at room temperature. The neutralized sample became negative (reading = 0.02) whilst the control sample remained positive (reading = 0.13). There was no other evidence of HBV infection as anti-HBc was negative, using a total antibody and IgM assay (VIDAS, Biomerieux, France). Fourteen days following immunization he was HBsAg negative using the same assay (reading = 0.02) and liver function tests remained normal. Routine dialysis in the chronic dialysis facility was re-commenced and he received the second dose of the hepatitis B vaccine after 3 weeks. Two months later he was still HBsAg negative (reading = 0.00) and the most likely explanation is that the EIA assay was detecting the vaccine HBsAg.
Haemopericardium associated with disruption of a clot using a flexible J-guide-wire in a haemodialysis catheter

Sir,

Central venous catheters are frequently used for haemodialysis vascular access. Total or partial clotting of these catheters requires a thrombolytic therapy or mechanical disruption. Haemopericardium is a rare complication of central venous catheter use. A 46-year-old female suffering from systemic lupus erythematosus with chronic renal failure was hospitalized to begin regular maintenance haemodialysis. Due to her poor vascular condition, an arteriovenous fistula was not possible. An arteriovenous graft was inserted, allowing for a normal dialysis session. During the following night, the patient complained of chest pain with severe dyspnea. Arterial blood pressure was 98/60 mm Hg and central venous pressure was 20 mm Hg. Echocardiography demonstrated pericardial effusion with patterns of tamponade. Pericardial drainage under general anaesthesia resulted in immediate good haemodynamic function. Thoracic radiographs of iodine contrast medium injected through the catheter showed the tip to be in contact with the cardiac wall. After this procedure the blood flow returned to normal, allowing for a normal dialysis session. The positive hepatitis B surface antigen test was detected on the second day post-implantation. The potential concentration available to be detectable was 55% of neonates given the vaccine and studied over 3 days. Four such infants were followed and HBsAg was detected in 65% with a peak at 2–3 days and a maximum at 8 days. Our present guidelines for the donation of blood products state that donation should not occur until 2 days after a hepatitis B immunization.

Both vaccines contain aggregates of the 24 000 kDa poly-peptide surface antigen adsorbed onto an alum carrier. If a proportion of the vaccine were to be free antigen then there is a chance this could find its way into the bloodstream to produce a positive result. The potential concentration available to the general circulation is certainly high enough at current assay limits to be detectable. Engerix B contains a higher concentration of HBsAg and along with differences in production may be the reasons why it has this propensity to be detected peripherally.

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Bone mineral density by quantitative digital radiography in patients with end-stage renal failure beginning replacement hemodialysis treatment and after one year of treatment

Sir,

All forms of bone disease in association with renal failure lead to a decrease in bone mineral density (BMD) [1]. It has been suggested that the BMD decrease is particularly manifest in the predialysis period, that hemodialysis (HD) at first slows this decrease [2], then after several years of HD treatment accelerates it again.

The aim of our study was to determine BMD in patients beginning replacement treatment with haemodialysis. The findings were correlated with the duration of renal failure prior to the introduction of replacement HD treatment, the concentration of intact parathyroid hormone (iPTH) in serum, and the condition after 1 year of HD treatment.

Our prospective clinical study included 18 patients (11 men and 7 women) with end-stage renal failure treated for one year at Maribor Teaching Hospital. For HD the Gambro AK 100 devices and Gambro GFS Plus 16 dialysers were used. The patients were dialysed in 3-weekly 4–5 h periods. The Ca content in dialysate was 1.5 mmol/l. BMD was measured by quantitative digital radiography (QDR) at the beginning of replacement treatment and after 1 year. A QDR 2000 plus device was used, belonging to the third generation of densitometers by Hologic and based on dual-energy X-ray absorptiometry. Bone density was measured at the left femoral neck as an example of cortical bone (BMDc).

The results are expressed in g/cm² and percent, whereby the normal value for the reference population on this instrument is 100%. The reference population consisted of healthy volunteers of suitable age and gender comparable to the dialysis patients.

iPTH was determined by means of the Allegro intact PTH immunoassay.

Description of results was by median ± standard deviation (SD), the minimum and maximum values were calculated. Statistical testing was by parametric statistical methods (t-test, correlation). P < 0.05 was considered a statistically significant finding. The statistical program by Statistica was used. The results are given in Table 1.

Our results show that at the beginning of replacement treatment with HD, BMDc is significantly lower than the predicted value in people of corresponding age and gender.

Table 1. mean patient age, duration of renal disease prior to treatment with haemodialysis, cortical bone mineral density (BMDc) (in % and g/cm²) at the beginning of treatment and after 1 year (BMDc1), intact parathyroid hormone concentration at the beginning of treatment (iPTH) and after 1 year (iPTH1) (n=11)

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49 ± 13</td>
<td>50 ± 12</td>
<td>47 ± 15</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>67 ± 40</td>
<td>60 ± 35</td>
<td>77 ± 45</td>
</tr>
<tr>
<td>BMDc (g/cm²)</td>
<td>0.67 ± 0.17</td>
<td>0.75 ± 0.12*</td>
<td>0.53 ± 0.14*</td>
</tr>
<tr>
<td>BMDc (%)</td>
<td>80.3 ± 16.1</td>
<td>88.7 ± 10.8*</td>
<td>67.1 ± 14.5*</td>
</tr>
<tr>
<td>BMDc1 (g/cm²)</td>
<td>0.66 ± 0.15</td>
<td>0.74 ± 0.13*</td>
<td>0.55 ± 0.11*</td>
</tr>
<tr>
<td>BMDc1 (%)</td>
<td>80.5 ± 14.7</td>
<td>87.6 ± 12.3*</td>
<td>69.3 ± 11.0*</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>316 ± 232</td>
<td>254 ± 170</td>
<td>414 ± 294</td>
</tr>
<tr>
<td>iPTH1 (pg/ml)</td>
<td>268 ± 243</td>
<td>238 ± 266</td>
<td>315 ± 212</td>
</tr>
</tbody>
</table>

*Statistical significance.

This means that a substantial amount of bone is already lost before the beginning of HD treatment. This fact is known from the literature [3]. Lindergard presented the average monthly decrease in BMDc 5 months prior to the beginning of HD treatment as −0.43% [3].

A negative correlation exists between the duration of renal disease prior to HD treatment and BMDc (g/cm² and %) in men (P < 0.05).

Urea kinetics (Kt/V) was used as a measure for HD adequacy. Kt/V over 1.2 was considered adequate HD.

After 1 year of replacement treatment with HD, the group of patients with Kt/V under 1.2 had a 2.2% decrease of BMDc, while the group with Kt/V over 1.2 had a 4.7% increase of BMDc (P < 0.05).

After 1 year our study shows an improvement of BMDc (+2.2% per year) in women. The cause probably lies in the fact that at the beginning of treatment two women with analgesic nephropathy had a very low BMDc (66±41% of predicted value), with high iPTH concentrations. In these two patients treatment with vitamin D (2 µg/dialysis) was introduced. Consequently BMDc increased in 1 year by 28 and 38% respectively. The phenomenon is explained by Heaf et al. [4]. Patients with a BMDc under 70% of the predicted value at the beginning of HD actually gain BMD after the introduction of treatment. The cause lies in the therapeutic effect of Ca in dialysate.

In our male patients the yearly decrease in BMDc was 1.1%. Such a decrease is also described by Heaf.

There was a statistically significant negative correlation between changes in iPTH concentration and changes in BMDc. This means that when there was a decrease in iPTH concentration there was also an improvement in BMDc.

In conclusion we may say that the measurement of BMD could not replace bone histology, especially regarding the evaluation of renal osteodystrophy. It is, however, a good method to monitor the evolution of bone disease.

Acknowledgements. The authors wish to thank Marijana Gajsek-Marchetti, translator, from the Medical Research Department, for her contribution in translating the present manuscript.

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Prevalence of latex sensitivity among patients with chronic renal failure—a new risk group?

Sir,

 Immunglobulin E (IgE) mediated hypersensitivity to natural rubber latex (NRL) has been recognized as an international medical problem due to wide use of latex products because of universal precautions. The prevalence of latex
allergy appears to be higher in certain risk groups due to increased exposure or to an increased intrinsic predilection for atopy [1,2]. Recently, crossreactive allergenic proteins have been identified in banana, avocado, chestnut, and kiwi [3–5]. Patients with CRF who are undergoing long-term dialysis can be assumed as an important risk group because of the various sources of exposure with latex gloves, catheters, adhesives, tourniquets, drains, and anesthetic equipment used during frequent hospitalization. In the present study we investigated latex sensitivity and also the relationship between latex and certain fruit allergens in CRF patients.

We studied a total of 268 patients (mean age 43.1 ± 15.1 years, with a range of 11–85 years). Of these subjects 159 were male and 109 female. All subjects were interviewed to determine the status and duration of their disease, frequency, and type of dialysis. Skin prick tests (SPT) were performed with latex, kiwi, banana and walnut extracts (Stallergènes S.A.-Pasteur, France). Serum samples were collected from each subject for determination of total IgE (Abbott Laboratories, IL). Data analysis was performed using SPSS for Windows. Patients were compared to a group of 26 healthy controls. A P value of <0.05 was regarded as significant.

Eight subjects claimed allergic symptoms related to rhinitis, 58 had dermatitis as a part of pruritis, but none had any reactions to latex products nor ethylene oxide sensitization. Of the patients tested, three (1.1%) had positive SPT results to latex antigen. Although one subject (33.3%) had positive SPT to kiwi antigen among latex sensitive subjects, a total of two had positive SPT results to kiwi and one to banana antigen in the latex negative SPT patients. None in control group showed latex sensitivity using SPT. When the results are taken together, the variables with no statistical significance (P > 0.05) included age, duration of renal disease, frequency of dialysis, and serum total IgE. However, all but one in SPT positive group were female.

In the general population, the prevalence of sensitization to latex proteins was estimated to be ∼3.5%. Particular groups of subjects have an increased incidence of allergic reactions to latex products [6,7]. Our results showed that a significant proportion of patients with CRF has negative SPT responses to latex despite frequent exposure. Host and environmental factors, including atopy and high levels of exposure—both occupational and non-occupational—can predispose to immunologic sensitization to latex [8,9]. This is further supported by the data of the present study demonstrating that none of the patients with latex positive SPT reported manifestations of atopic diseases nor had high IgE concentrations.

In this study, the prevalence of latex positive SPT in CRF patients is lower compared to other reported risk groups. One of the major differences is that our group consisted of patients with different dialysis programs equally, since the exposure to latex products varies. Alternatively, in other studies, more symptomatic subjects may have participated. By contrast, in our study, we tried to avoid this voluntary participation by inviting almost all dialysis patients. Another explanation for the difference in response rates may reflect various allergen content in the latex extract used, since allergenicity varies from one product to another.

The most striking finding in this study was the clear predominance of middle-aged woman among latex and fruit positive SPT subjects. Latex allergens are ubiquitous, and exposure may occur from different sources in the medical equipment as well as in daily life [8]. Female predominance in our data could be explained with frequent use of household latex products. Moreover considerable crossreactivity between NRL and certain fruit allergens can be assumed as one subject (33%) of latex positive SPT patients had positive reaction to kiwi compared to a total of three in the latex negative SPT individuals.

In conclusion, CRF patients with no history of hypersensitivity reactions despite recurrent latex exposure cannot be assumed as a risk group for developing latex sensitization. Although sensitivity to latex is thought to be more common than previously suspected, the predictive value of screening with SPT is not known in risk groups. Diagnosis of clinically relevant allergy depends, in the first instance, on a correlation between the clinical history and the results of skin tests. Thus, if there is a patient with no history of latex allergy, but has a positive SPT response, he or she may be followed up closely. However, if symptoms are present, latex allergy must be diagnosed by testing, otherwise precautionary latex avoidance measures should be undertaken empirically.

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Is there a female predominance in popliteal cysts in long-term haemodialysis patients?

Sir,

The development of popliteal cysts (PC) has recently been reported as a manifestation of dialysis-related amyloidosis [1–5]. We read with great interest the recent case report by Dantoine T et al. [1] on a female long-term haemofiltration/haemodialysis patient with PC due to dialysis-related amyloidosis. The authors report that the formation of PC is an extremely rare manifestation. We experienced PC rather frequently in long-term haemodialysed patients treated with high-flux membrane dialysers. Moreover, we had a vague impression that there might be a female predominance in PC.

To confirm these matters, we carried out a physical and ultrasonographical screening for PC in 66 patients with chronic renal failure undergoing maintenance haemodialysis for more than 10 years (an average of 18.8 ± 4.4 years), with different types of high-flux membrane dialysers. They consisted of 33 males and 33 females, the mean age being
Female patients, and has female predominance in long-term haemodialysis. Lactate 3.3 mmol/L was detected in 4 males and 20 females. We analysed the data from Baldrati et al. [4] that had no sex difference by $\chi^2$ test.

Patients data are summarized in Table 1. PC was detected in 15 out of 66 patients (22.7%). Both groups with and without PC were essentially the same with respect to mean age (60.4±8.6 vs 57.9±8.3 years), average duration of haemodialysis (19.4±4.5 vs 18.8±4.4 years) and primary renal diseases. PC was observed in 2 out of 33 males (6.1%) and 13 out of 33 females (39.4%) ($P<0.01$). All of them could not sit straight. In 10 patients with PC who were investigated with CT, PC and the knee joint cavity were in contact. The knee joint cavity was filled with fluid collection with few septum. On T1-weighted images, PC showed a high signal intensity. Due to analgesic nephropathy, on chronic haemodialysis for 8.3 years, none of them had amyloid nephropathy or renal involvement due to rheumatoid arthritis. To clarify the characteristics of PC, we examined with computed tomography (CT) and magnetic resonance imaging (MRI). MRI was performed on a 1.5-Tesla, whole-body, superconducting unit (Magnetom H15 Siemens) using spin-echo techniques with two data acquisitions per imaging period. PC were associated amyloidosis presenting as bilateral popliteal tumors. Am J Kidney Dis 1990; 2: 444–445. MRI studies demonstrated that PC appeared as well-defined fluid collection with few septum. On T1-weighted images, PC had a signal intensity slightly lower than that of muscle. On T2-weighted images, PC showed a high signal intensity. In three patients who were investigated by needle biopsy, free amyloid fibrils were seen with Congo-red stain and positive for $\beta_2$-microglobulin by immunohistochemical analysis.

Baldrati et al. [4] detected PC in 6 of 28 patients (21.4%) on haemodialysis for more than 60 months. According to the previous reports [1–5] and the present study, PC was detected in 4 males and 20 females. We analysed the data from Baldrati et al. [5] that had no sex difference by $\chi^2$ test.

The present study indicated that PC is not a rare lesion and has female predominance in long-term haemodialysis patients.

<table>
<thead>
<tr>
<th>PC (+)</th>
<th>PC (−)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n=66)</td>
<td>15</td>
<td>51</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.4±10.2</td>
<td>57.4±9.8</td>
</tr>
<tr>
<td>Duration of haemodialysis (years)</td>
<td>19.6±4</td>
<td>18.6±4.9</td>
</tr>
<tr>
<td>Prevalence of PC</td>
<td>15/66 (22.7%)</td>
<td>31</td>
</tr>
<tr>
<td>Male patients (n=33)</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.4±9.3</td>
<td>57.5±8.9</td>
</tr>
<tr>
<td>Duration of haemodialysis (years)</td>
<td>17.7±9.5</td>
<td>19.4±4.9</td>
</tr>
<tr>
<td>Prevalence of PC</td>
<td>2/33 (6.1%)</td>
<td>31</td>
</tr>
<tr>
<td>Female patients (n=33)</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.1±10.5</td>
<td>56.5±11.2</td>
</tr>
<tr>
<td>Duration of haemodialysis (years)</td>
<td>19.7±4.9</td>
<td>17.3±4.8</td>
</tr>
<tr>
<td>Prevalence of PC</td>
<td>13/33 (39.3%)</td>
<td>31</td>
</tr>
</tbody>
</table>

PC: popliteal cyst. *$P<0.01$, significant difference in prevalence of PC between male patients and female patients by $\chi^2$ test.

Again: segmentary necrosis of the ascending colon (SNAC) in a chronic haemodialysis patient

Sir,

In recent years there has been an intriguing number of reports on ischaemic bowel disease in chronic renal failure patients [1–4]. We present another case.

A 64-year-old female patient with end-stage renal disease due to analgesic nephropathy, on chronic haemodialysis for 2 years, was admitted to our hospital for a history of severe abdominal pain starting the evening before. In addition, she complained of nausea and vomiting, and her body temperature was 38°C. Her last bowel movements 2 days before had been normal. Clinical examination revealed diffuse tenderness of the abdomen with a punctum maximum in the right lower quadrant. Blood pressure was 120/60 mm Hg. A plain film of the abdomen disclosed a meteoristic colon. Ultrasound examination demonstrated a hydropus of the gallbladder. WBC count was 16,700/mm³, lactate 3.3 mmol/l.

An enema was given, but no stool was produced. During the following hours her abdominal pain worsened. Due to local defense and rebound tenderness, a surgical intervention was performed. The operating surgeon detected a circumscript necrosis of the ascending colon in an extent of 10×5 cm and a few small necrotic foci in the area of the right colonic flexure; the gallbladder appeared normal. A right-sided hemicolectomy was performed. The postoperative course of our patient was uneventful. She left the hospital on the 11th postoperative day. The histopathological findings were necrosis of the complete colonic wall and a non-specific necrosis of the complete colonic wall and a non-specific.
inflammation of six lymph nodes. No mesenteric vessel obstruction was noticed.

Some of the known predisposing factors could be identified: a preceding abdominal operation (appendectomy 57 years ago), regular use of sedatives, long-standing hypertension and chronic heart failure. But most risk factors like overt atherosclerotic disease, diabetes mellitus, hypercholesterolaemia, confinement to bed, a recent surgical procedure under general anaesthesia, the use of digoxin, aluminium-hydroxide based phosphate binders, use of ergotamine, vasopressors, corticosteroids, or laxative agents as well as triggers like hypotensive episodes caused by excessive intradialytic fluid loss, an acute cardiac problem or non-dialytic volume depletion from diarrhoea were absent.

Occlusive atherosclerotic disease, a known complication of analgesic nephropathy (5), may have contributed to the development of the bowel ischaemia.

In summary, our patient presented with a non-occlusive segmental necrosis of the ascending colon. Adequate surgery was performed within 24 h after the onset of pain, leading to full recovery.

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Cervical myxofibrosarcoma in a renal allograft recipient treated with murine anti-CD3 monoclonal antibody therapy

Sir.

Myxofibrosarcomas are soft tissue neoplasms, usually arising in elderly patients, especially in the limbs (1). Cytomegalovirus infection has been implicated in the oncogenesis of an infantile form of the tumour (2). We wish to report a 43-year-old renal allograft recipient who developed a localized low grade cervical, myxofibrosarcoma 6 years after transplantation. He presented at the age of 37 in 1991 with end-stage renal failure and bilaterally small kidneys. The cause of his renal failure was uncertain, although he had been diagnosed as suffering from mild hypertension 1 year earlier, and he also had a history of gout dating from his mid-twenties. Shortly before starting dialysis, in June 1991, he underwent cadaveric renal transplantation. Induction immunosuppression was with 500 mg methylprednisolone and 2 mg/kg of cyclosporin A given intravenously. Good primary function was followed by an episode of mild vascular and moderate cellular rejection which was treated with 1 g of parenteral methylprednisolone on three consecutive days. A second episode of early graft dysfunction was treated with 10 days of 5 mg murine monoclonal anti-CD3 antibody (OKT3, Cilag Biotech), following which graft function stabilized at creatinine 210 μmol/l. Azathioprine at 2 mg/kg was added in August 1991 and continued until recurrent gout necessitated the introduction of allopurinol in August 1996, when the azathioprine was stopped. The patient developed bilateral femoral head avascular necrosis in November 1991. The recipient had positive cytomegalovirus (CMV) titres at the time of transplantation, and there were no clinical manifestations of reactivation.

All was well until February 1997 when, now aged 43, the patient presented with a 2-week history of a discrete, painless lump on the right side of his neck. The lump was solid, spheroid, non-mobile and approximately 1.5 cm in diameter. An urgent surgical exploration exposed a lobulated, grey mass, which was removed. Histopathological examination revealed a predominantly myxoid lesion, with scattered curved, thick walled blood vessels and variable cellularity. Some of the cells were spindle cells and some polygonal with cytoplasmic vacuolation. There was mild to moderate nuclear pleomorphism and occasional mitotic figures. Immunohistochemical testing was negative for S100 protein, smooth muscle actin, desmin and cytokeratin, and a diagnosis of low grade myxofibrosarcoma (myxoid malignant fibrous histiocytoma) was made. Histological examination of a further local clearance showed that excision appeared complete. No evidence of local recurrence has been evident on subsequent follow up.

Fig. 1. Photomicrograph of tumour showing typical curved vessels and pleomorphic spindle cells, some of which are vacuolated, dispersed in a myxoid stroma.

The occurrence of myxofibrosarcoma has not to our knowledge been previously reported in a transplant recipient. A recent analysis of 75 cases shows that they tend to occur in elderly adults, with a median age of 66 years (3). The usual site of origin is in the limbs (1), occurring in 65% of reported cases, while only 3% occur in the head and neck (3). As in this case, most arise adjacent to or from within dermal tissue. Whilst local recurrence occurred in 54%, irrespective of grading, metastasis was not reported in 60 patients with low grade forms, followed for 45 months (3). The tendency to local recurrence appears to relate not to initial depth, but to the diffuse and infiltrating nature of the
primary tumour as illustrated in an unusual report of the malignancy in a Japanese teenager [4] as well as in our own case. After local recurrence however myxofibrosarcoma tends to progress in grade [3].

The role of anti-CD3 therapy in inducing lymphoproliferative disorder and lymphoma is well recognized, particularly in association with Epstein Barr virus (EBV) or CMV infection [2,5]. While this tumour does occur in immunocompetent individuals and may have arisen by chance, it is tempting to speculate that the high immunosuppressive burden may have predisposed to the development of this tumour.

The potential role of CMV infection is more speculative, given that concomitant cytomegalovirus infection has been proposed as a contributor to the pathogenesis of fibrosarcoma presenting in infants [6]. However our patient showed no overt clinical manifestations of CMV or EBV infection during treatment for rejection, and the CMV titre remained unchanged from before presentation with the tumour. We could not demonstrate the presence of inclusion bodies in the pathological specimen, and no unfixed tissue was available for in situ localization of viral genomic material. However, the long term persistence of herpes viruses in many tissues makes it difficult to completely exclude a role for CMV in the aetiology of this condition.

Given the widespread use of monoclonal anti-rejection therapy, new presentations with myxofibrosarcoma may be anticipated. Vigorous local resection to ensure complete excision is mandatory. To date, our patient remains well, but further case reports would be instructive to help define the natural history of such tumours in immunosuppressed organ recipients.

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