Neuromuscular complications of kidney diseases

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Introduction

The uraemic syndrome is characterized by overall deterioration of biochemical and physiological functions in parallel with the progression of renal failure. Uraemia results in variable symptoms pointing to damage of multiple organs, due to retention of compounds normally cleared by the healthy kidneys [1]. The identified mechanisms currently are attributed to increased protein catabolism, reduced excretory capacity and altered water–electrolyte homeostasis [2]. Major neurotoxins accumulating in uraemia are urea, creatinine, guanidine compounds, a number of aromatic acids, uric and ossalic acids, myo-inositol, ‘middle molecules’, β₂-microglobulin, amines and parathyroid hormone (PTH) [2]. The nervous system, both central and peripheral, may show changes, mimicking exogenous poisoning or drug overdose [1]. Here we review the clinical, electrophysiological and morphological aspects of peripheral nervous system syndromes related to kidney failure, focusing principally on practical implications for the daily management of patients (Table 1). The growing knowledge about the clinical approach of these disorders underscores the importance of their early recognition, as precise identification is crucial for treatment strategies.

The neuropathies of kidney failure

Uraemic polyneuropathy

Despite the beneficial effects of haemodialysis and successful renal transplantation, uraemic polyneuropathy represents a well-known complication of end-stage renal failure (Table 2). It should be regarded as an indicator of the degree of renal failure and its control by haemodialysis. Uraemic polyneuropathy has to be distinguished from other types of neuropathy occurring in chronic uraemia, such as diabetes [2–4]. Previous works have gathered detailed descriptions on clinical, electrophysiological and morphological aspects of uraemic polyneuropathy [2,3,5–8]. The incidence of clinical polyneuropathy varies considerably from series to series, ranging from 10 to 83%, with males more affected than females [2,6]. Bolton pointed out that 60% of patients receiving haemodialysis for uraemia have neuropathy by electrodiagnostic criteria [2]. The main symptoms are restless legs, spontaneous cramps, distal paresthesias, numbness and burning feet, which, however, are not necessarily related to the neuropathy, but due possibly to transient disturbances of peripheral sensory receptors, induced by fluctuation in water and electrolytes [2]. Symptoms may occur either prior to or during a regular haemodialysis programme; the latter could indicate that the achieved control is not optimal [2,3]. Clinical signs of uraemic polyneuropathy include symmetric muscle weakness, areflexia and sensory loss for all modalities, especially pin-prick and vibration. An early finding is elevation of the vibratory central and peripheral, may show changes, mimicking exogenous poisoning or drug overdose [1]. Here we review the clinical, electrophysiological and morphological aspects of peripheral nervous system syndromes related to kidney failure, focusing principally on practical implications for the daily management of patients (Table 1). The growing knowledge about the clinical approach of these disorders underscores the importance of their early recognition, as precise identification is crucial for treatment strategies.

Pathology of uraemic polyneuropathy

In 1963, Asbury [7] published four autopsy cases affected by different types of renal diseases previously untreated with haemodialysis, so that their neuropathy was entirely due to kidney failure. Pathological changes were consistent with degeneration of distal nerve trunks in a dying-back fashion [6,7]. In addition, the finding of chromatolysis in the anterior horn cell bodies in the spinal cord indicated a primary lower neuron damage. Said et al. studied 10 uraemic patients at various stage of renal failure, and confirmed a variety of pathological changes, including axonal loss with secondary demyelination or predominant demyelination [9]. Dyck et al. [5] and Thomas et al. [8], from teased fibre studies, confirmed the evidence of primary distal axonal neuropathy, with secondary demyelination. According to clinical symptoms and signs presented by the patients, distinct types of uraemic polyneuropathy can be identified; the course can be either chronicly progressive (Table 2), subacute or acute and fulminant (Table 3) [2,4,6,9–12]. Pathological observations in sensory nerves demonstrated, in the acute axonal form, wallerian-like changes associated with segmental and paranodal demyelination [9]. In other cases, extensive abnormality of myelin sheaths with abundant macrophage infiltration seemed consistent with primary Schwann cell and myelin pathology [2,9,11]. In all

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Table 1. Peripheral neuropathies complicating kidney failure

<table>
<thead>
<tr>
<th>Subclinical neuropathy</th>
<th>Mononeuropathy</th>
<th>Multineuropathy</th>
<th>Polyneuropathy</th>
<th>Autonomic neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>By electrophysiological criteria</td>
<td>Entrapment (median, ulnar, peroneal, radial nerves) cranial nerves V, VII, VIII</td>
<td>Proximal diabetic</td>
<td>Chronic distal symmetric</td>
<td>Controversial occurrence, usually associated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During systemic vasculitis, entrapment, ischaemia, at multiple sites</td>
<td>sensori-motor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Subacute progressive</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Acute, fulminant</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Relapsing (?)</td>
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</tbody>
</table>

Table 2. Features of chronic uraemic polyneuropathy: symptoms and signs

| Motor weakness (UE, LE), wasting, hypoareflexia | Sensory ataxia | Cramps | Paresthesias | Sensory loss: vibration, pain, position, pin-prick, temperature | Orthostatic hypotension | Impotence | Diarrhoea | Constipation | Incontinence | Abnormal tilt test, Valsalva manoeuvre | Denervation at rest, loss of MUPs, ↓ recruitment (needle EMG) | Normal or increased (up to 1–2 g/l) | Cells/mm³: usually absent | Nerve biopsy: Distal axonal loss | Secondary demyelination (segmental, paranodal) | Wallerian-like degeneration | Regeneration | β₂-microglobulin amyloidosis | Muscle biopsy: Fibre atrophy | Tendency to type grouping | Unremarkable inflammatory changes | Chronic evolution or worsening (concurrent illness) | Stable condition | HD/CAPD | HDF: stable plateau | Transplantation: clinical electro-physiological improvement |
|-------------------------------------------------|----------------|--------|-------------|-----------------|------------------|--------|---------|---------|---------|----------------|------------------|------------------|----------------|-------------------------|-----------------|-----------------------|---------------|------------------------|------------------------|----------------------|---------------|----------------------|---------------|----------------------|
Neuromuscular complications of kidney diseases

Patterns, degeneration of distal axons is followed by regeneration, sprouting and regrowth of proximal axons [2,6,9]. Segmental demyelination accounts for the slowing in nerve conduction velocity along motor and sensory nerves in uraemic polyneuropathy, whereas the axonal regrowth explains clinical improvement after dialysis treatment or renal transplantation [2]. The progression rate of uraemic polyneuropathy varies considerably, most commonly worsening and recovery evolve over months [2,6]. In 1992, Ropper [11] described four diabetic patients receiving peritoneal dialysis affected by an acute syndrome characterized by limb weakness progressing over days or weeks, severe ataxia, diminished reflexes and raised cerebrospinal fluid (CSF) protein. Electrophysiology suggested extensive demyelination, secondary to the distal large fibre degeneration and loss, emphasized by previous reports [5–9]. This neuropathy improved in two patients with more frequent peritoneal dialysis and with transplantation, whereas it worsened in the remaining two, where diabetes could have a role [11]. Bolton et al. [12] reported in 1997 a subacute, predominantly motor axonal polyneuropathy in four diabetic uraemic patients. Unfortunately, the sural nerve was not biopsied. In 1990, we described an uraemic patient, who developed a severe polyneuropathy characterized by external ophthalmoparesis, trunk and extremity ataxia, limb weakness, areflexia and high CSF protein, with electrophysiological evidence of a conduction block in the arms and legs [13]. Neurological symptoms waxed and waned in the early phase of the patient’s illness, apparently in relation to the haemodialysis schedule, resembling the disequilibrium syndrome; the latter suggested that functional changes such as occur in early experimental diabetes might precede the phase of ‘structural dysfunction’ with persistent damage [14].

Electrophysiology of uraemic polyneuropathy
Electrophysiology in uraemic polyneuropathy confirms the clinical evidence of autonomic dysfunction, with abnormal Valsalva manoeuvre, tilt test and R–R interval [2]. In addition, there are documented cases of slowing in conduction velocity along motor and sensory nerves, prolonged proximal and distal latencies and reduced amplitude of compound action potentials, even in the absence of clinical neuropathy [2]. Bolton and Nielsen’s studies defined the electrophysiological indicators of the treatment effectiveness and stated that to prevent uraemic polyneuropathy, chronic haemodialysis should be started early when a residual renal function is preserved [2,15]. In 56 uraemic patients not receiving regular haemodialysis, Nielsen demonstrated a high correlation between diminishing creatinine clearance and the falling conduction velocity, which tends to occur when creatinine clearance is reduced to ~10% of normal [15]. Conduction continues to slow as renal function worsens [2,6,15]. The physiological basis of slowing was due to inhibition of axonal membrane function due to accumulation of uraemic metabolites [2,6]. The reduced axonal transport causes diminished
axonal resting membrane potential and impaired impulse propagation [2,3]. Experimental observations confirmed a crucial role for lowered axoplasmic sodium content and sodium permeability of the nodal membrane [16]. Scribner et al. [17] introduced the concept of ‘middle molecules’ ranging from 300 to 2000 Da, acting as neurotoxins and not removed by the dialysis membranes. Brugger et al. in 1983, using in vitro methods, showed that tubulin, an intracellular protein that polymerizes axon microtubules, is inhibited by ‘middle molecules’ of uraemia [18]. After considerable investigations to assess the long-term effects of intermittent dialysis on uraemic polyneuropathy, a general consensus emerged that some patients unpredictably might either stabilize, improve slowly or get worse, especially in the presence of concurrent sepsis, diabetes and other systemic illnesses which can contribute to superimposed critical illness polyneuropathy [2,6]. Chronic haemodialysis, continuous ambulatory peritoneal dialysis (CAPD), and haemodiafiltration (HDF), however, stabilize peripheral nerve function in the large majority of cases, whereas renal transplantation usually produces a recovery phase over a 6–12 month period, due to remyelination and axonal regeneration [6]; autonomic function may also be restored to normal. In subclinical neuropathy, nerve conduction abnormalities often persist, regardless of the type of dialysis programme used [2,3,6].

Mononeuropathy

The peripheral nerves of uraemic subjects are susceptible to local or multiple site ischaemia and compression. The most common mononeuropathy is the carpal tunnel syndrome, which initially was attributed to the vascular shunt on the upper arm between the brachial artery and antebrachial vein, also causing associated radial and ulnar neuropathies [2,6]. Charra et al. [19] demonstrated amyloid deposits in connective tissue and tendons, surrounding the carpal tunnel of uraemic patients. Recently, Shirahama et al. [20] showed that the amyloid of chronically dialysed uraemic patients derived from β2-microglobulin not cleared by the kidney. Due to reduced renal function, β2-microglobulin accumulates, causing joint symptoms and pathological fractures. Management of carpal tunnel syndrome is based on surgical release. The common peroneal nerve can also be compressed at the fibular head. Among cranial nerves, cochlear–vestibular and facial dysfunction are described [2].

Myopathies in renal failure

During renal failure, muscle weakness may develop in relation to cachexia, sepsis, steroid treatment and water–electrolyte disturbances [2]. Clinical features in the latter cases resemble the acute periodic paralysis associated with hypo- or hyperkalaemia. In addition, because of elevated phosphate retention and altered PTH and vitamin D metabolism, uraemic patients may exhibit a severe painful myopathy [21] (Table 4). A possible explanation for the effects of PTH on muscle could be interference with the mitochondrial calcium permeability, producing a net influx of calcium from the mitochondria and reduced calcium sensitivity of the contractile system [21]. In addition, the inability to convert 25-OH-D3 to the active form of cholecalciferol causes reduced calcium uptake by the sarco-plasmic reticulum and impaired myofibrillar ATPase activity [21]. Muscle biopsy in secondary hyperparathyroid myopathy reveals type II fibre atrophy, Z-line unspecific abnormalities, calcium deposits in the necrotic fibres and ischaemic changes, due to altered perfusion by vessel calcification and narrowing [21].

Peripheral neuropathies associated with kidney failure

Disorders of peripheral nerves and skeletal muscles may develop in the setting of systemic necrotizing vasculitides, which are a heterogeneous group of diseases having an immunologically mediated mechanism and inflammatory pathology [22,23]. Brain, skin, lung and kidney can be affected. The kidney is damaged either directly or secondarily to development or aggravation of hypertension [2]. Systemic necrotizing vasculitides, although differing in aetiopathogenetic mechanism, clinical manifestation, outcome and response to treatment, share a common pathology [22,23]. The morphological hallmarks are transmural inflammatory cell infiltration, and fibrinoid necrosis in the media of affected vessels showing segmental narrowing, occlusion and perivascular inflammatory cell infiltration [22,23] (Figure 1). Necrotizing vasculitides have been classified pathologically, according to the size of affected blood vessels, or in clinical and aetiological terms [22,23]. The peripheral nervous system commonly is affected [24–31]. Nerve damage is due to occlusion of the vasa nervorum, leading to axonal degeneration, segmental demyelination and fibre loss [24,28].

Immunopathogenesis of vasculitis is controversial: three putative mechanisms are implicated. The classical theory supported by experimental models involves a leukocytoclastic reaction in the vessel wall. Circulating immune complex deposition in the vessel walls activates the complement cascade and the release of lysosomal enzymes. A second hypothesis proposes a cell-mediated process, with interaction between T-lymphocytes and endothelial cells secreting cytokines, which ultimately trigger a cytotoxic inflammatory response [22,24,26–31]. Sural nerve infiltrates in these cases are composed primarily of CD8 lymphocytes and macrophages, with few or any neutrophils [29]. A third mechanism involves antibodies against specific cellular antigens, the anti-neutrophil cytoplasmic antibodies (ANCAs) especially found in sera of patients with Wegener’s granulomatosis (WG), classic polyarteritis nodosa (c-PAN) and microscopic polyangiitis (MPA) [22,31,32]. ANCAs are considered to reflect the
Table 4. Myopathies in uraemia

<table>
<thead>
<tr>
<th>Clinical syndromes</th>
<th>Symptoms and signs</th>
<th>Electrophysiological features</th>
<th>Pathology (muscle biopsy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periodic paralysis</td>
<td>Profound muscle weakness</td>
<td>Spontaneous repetitive discharges, at rest</td>
<td>Type II atrophy</td>
</tr>
<tr>
<td>Steroid myopathy</td>
<td>Atrophy</td>
<td>Polyphasic MUPs</td>
<td>Lipid droplets</td>
</tr>
<tr>
<td>End-stage renal, cachectic</td>
<td>Muscle tenderness</td>
<td>Full recruitment, low voltage</td>
<td>Vessel changes</td>
</tr>
<tr>
<td>Hyper-PTH myopathy</td>
<td>Exertional muscle pain normal or ↑ CPK</td>
<td>Associated sensorimotor neuropathy</td>
<td>(calcium deposits, intimal proliferation)</td>
</tr>
<tr>
<td>Myoglobinuria</td>
<td></td>
<td></td>
<td>Necrotic/ischaemic changes</td>
</tr>
</tbody>
</table>

Fig. 1. Necrotizing vasculitis of a large epineurial artery in a case of PAN. There is a dense mononuclear cell infiltration, intimal proliferation and occluded lumen. (Paraffin-embedded section, H&E stain. Original magnification × 150.)

involvement of small-sized vessels, as their titres have shown a correlation with disease activity and rise before clinical relapses [22,32]. The main antigenic targets for ANCAs are proteinase 3 (PR3) and myeloperoxidase (MPO). The current hypothesis for the ANCA pathogenetic mechanism is that these autoantibodies induce neutrophil activation, leading to release of toxic proteases, including PR3 and reactive oxygen species, which could induce the vasculitic lesions [32]. Usually, vasculitic neuropathy presents as a multiple mononeuropathy with abrupt onset of pain and weakness in the distribution of the affected nerve, tingling paresthesias and sensory loss, especially for pain and temperature, as the smallest fibres are more vulnerable to ischaemia than the largest ones [24,25]. The condition can be easily recognized, or can be less distinctive when the patient has no evidence of multiorgan abnormalities. In contrast to proven electrophysiological mononeuritis multiplex, 34–67% of the cases had no evidence of connective tissue disease [25]; over 10% of cases with vasculitic neuropathies may develop during the course of other systemic illnesses, such as remote malignancies, hepatitis B and HIV infections [22,25]. In mononeuritis multiplex, the distribution of nerve infarction is not random, as some nerves can be especially predisposed, e.g. the median, ulnar, peroneal, tibial and sural [24,28,30,31]. Vasculitic neuropathy can present also with generalized distal symmetric polyneuropathy or with mononeuritis multiplex [28]. Nerve conduction studies typically reveal a low amplitude of sensory nerve and compound muscle action potentials in a multifocal or diffuse distribution, with the maximal velocity normal or minimally reduced. Needle EMG usually shows acute, partial denervation and loss of motor units in weak muscles [28]. The diagnostic yield of muscle and nerve biopsies is high, especially if directed at electrodiagnostic abnormalities [24,25].
The polyarteritis nodosa group of systemic necrotizing vasculitides in Fauci’s classification [23] comprises c-PAN, the Churg–Strauss syndrome (CSS) and an overlap angitis, with confirmed signs of involvement in at least two organ systems (MPA) [22,25]. A peripheral neuropathy develops in 44–60% of patients, and the presenting symptom in one-third of the patients is within the first year of illness [28]. Single or multiple mononeuropathies are more common than distal symmetrical polyneuropathy [24,25,28,31]. Patients have typical complaints of weight loss, myalgias and arthralgias; cutaneous signs, fever, hypertension, renal, cardiac and gastrointestinal signs are common. Laboratory signs include elevated sedimentation rate, anaemia, leukocytosis, the presence of hepatitis surface antigen, low C₄ and C₃ titre [25,28,31]. The c-PAN vasculitis affects medium-sized arteries. The involvement of the kidney is the consequence of renal vasculitis and of multiple infarcts [2,22,25]. Abdominal and renal angiogram can show microaneurisms and segmental narrowing. Untreated patients have a 6 month survival rate of 35% and a 5 year survival rate of 13% [25]. Steroid therapy and early use of cyclophosphamide has allowed 5 year survival rates of up to 76–80% [22,25,33,34]. MPA, formerly called microscopic polyarteritis nodosa, is characterized histologically by the involvement of small-sized arteries and clinically by the presence of glomerulonephritis, leading rapidly to severe renal insufficiency and failure. Anti-MPO ANCs are detectable [22,32]. Pulmonary involvement, consistent with capillaritis and alveolar haemorrhage, occurs in one-third of cases [22]. CSS, clinically characterized by asthma and eosinophilia (>1500 mm³) and histologically by medium-sized vasculitis and extravascular granuloma, can be associated with peripheral neuropathy, most frequently in a multifocal pattern [33,34]. ANCs have been detected in half of patients with CSS [22]. In WG, the vasculitis involves medium and small-sized arteries, veins and capillaries, with pathological evidence of granulomas. Lung, ear, nose, throat, kidney and peripheral nerves can be affected [35]. The neuropathy occurring in 11–16% of cases is usually multifocal or, in late cases, symmetrical. ANCA is the immunological marker of the disease, being detectable in 80–90% of systemic and in half of the localized forms [22,25].

Systemic necrotizing vasculitis with vasculitis neuropathy also complicates connective tissue diseases, with possible kidney involvement, such as in rheumatoid arthritis, where neuropathy can be the presenting symptom in 40–50% of patients. This neuropathy clinically, pathologically and electrophysiologically is almost indistinguishable from that of c-PAN [36,37]. In 6–21% of systemic lupus erythematosus patients typically there is a distal symmetrical polyneuropathy, with predominantly sensory symptoms, acute or subacute evolution, axonal degeneration and occasional demyelination [38,39]. Peripheral sensorimotor neuropathy in a distal symmetric pattern is present in 10–20% of cases with Sjögren’s syndrome [40,41] and in 14% of systemic sclerosis patients [25,42]. Recently, the hepatitis C viral infection has been implicated in the disease process of essential mixed cryoglobulinaemia associated with type II and III mixed cryoglobulins. Cryoglobulins result in circulating immune complexes, responsible for chronic angitis, whose major symptoms are purpura, arthritis, glomerulonephritis and sensorimotor peripheral neuropathy, due to multifocal vasculitis [22,43]. In conclusion, recognition and clinical care of peripheral nerve systemic vasculitis is particularly challenging for clinicians, as therapeutic strategies must be directed towards the pathophysiological identification of the underlying disease process [22].

References

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