Neurological complications of chronic kidney disease

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Abstract | Chronic kidney disease (CKD) is a critical and rapidly growing global health problem. Neurological complications occur in almost all patients with severe CKD, potentially affecting all levels of the nervous system, from the CNS through to the PNS. Cognitive impairment, manifesting typically as a vascular dementia, develops in a considerable proportion of patients on dialysis, and improves with renal transplantation. Patients on dialysis are generally weaker, less active and have reduced exercise capacity compared with healthy individuals. Peripheral neuropathy manifests in almost all such patients, leading to weakness and disability. Better dialysis strategies and dietary modification could improve outcomes of transplantation if implemented before surgery. For patients with autonomic neuropathy, specific treatments, including sildenafil for impotence and midodrine for intradialytic hypotension, are effective and well tolerated. Exercise training programs and carnitine supplementation might be beneficial for neuromuscular complications, and restless legs syndrome in CKD responds to dopaminergic agonists and levodopa treatment. The present Review dissects the pathophysiology of neurological complications related to CKD and highlights the spectrum of therapies currently available.

Krishnan, A. V. & Kiernan, M. C. Nat. Rev. Neurol. 5, 542–551 (2009); published online 1 September 2009; doi:10.1038/nrneurol.2009.138

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Learning objectives
Upon completion of this activity, participants should be able to:
1. Describe the relationship between cognitive impairment and chronic kidney disease.
2. Manage restless legs syndrome appropriately among patients with chronic kidney disease.
3. Diagnose uremic neuropathy effectively.
4. Treat neuropathy effectively among patients with chronic kidney disease.

Introduction
Chronic kidney disease (CKD) is a rapidly growing global health problem, with a prevalence of 15% in developed nations.1–4 In the US alone, more than 400,000 individuals have end-stage kidney disease (stage 5 CKD; Box 1) and are currently receiving dialysis treatment.5 CKD can occur as the result of a primary renal disorder or as a complication of multisystem disease. Diabetes is now the most common cause of CKD in developed countries,6 whereas in the developing world, inflammatory diseases of the kidney, particularly glomerulonephritis and interstitial nephritis, remain the most common causes.7 CKD encompasses a spectrum of disease, ranging from mild kidney damage, which can be asymptomatic and is only detected by blood and urine testing, through to end-stage disease, in which kidney function is impaired to such an extent that the retention of metabolic waste products, salt and water becomes potentially fatal.8 A neurologist who is asked to consult on a CKD patient is likely to be faced with several systemic features. Fluid retention can manifest as peripheral edema and congestive cardiac failure, and retention of toxic solutes, notably urea and potassium, can lead to changes in skin pigmentation, pericarditis and cardiac arrhythmia. A range of metabolic disturbances has also been noted in CKD, including insulin resistance, amenorrhea, and bone disease due to the combined effects of hyperparathyroidism, phosphate retention and vitamin D deficiency.9 From a neurological perspective, clinical features of CKD include weakness and length-dependent sensory impairment, which lead to functional disability, and, in patients with acute uremia, an altered mental state due to encephalopathy.

When renal function reaches critically low levels, renal replacement therapy is required, either in the form of dialysis or transplantation. A five-stage system based on the estimated glomerular filtration rate—a measure of renal function derived from the patient’s serum creatinine level,
Patients on dialysis tend to be weaker and less active, and to have reduced exercise capacity, when compared with healthy individuals.1,11,12 These physical limitations can frequently be attributed to the neurological complications that develop in almost all patients with CKD and affect all levels of the nervous system (Figure 1).13–16 From a public health perspective, the development of definitive treatment strategies for the neurological complications of CKD is, therefore, a matter of priority. This Review will provide an overview of the clinical features and pathophysiology of, and treatment strategies for, the most common neurological complications of CKD, which include cognitive dysfunction, stroke, restless legs syndrome (RLS), peripheral and autonomic neuropathy, mononeuropathy, and myopathy (Table 1).

Uremic toxins and neurological disease

The uremic state of CKD is characterized by the retention of solutes that are toxic in high concentration, such as urea, creatinine, parathyroid hormone, myoinositol, and β2-microglobulin.9 Studies investigating the pathophysiology of neurological disease in CKD have tended to focus largely on the hypothesis that one or more of these retained toxins is responsible for mediating the neurological dysfunction. This hypothesis has been supported by studies that demonstrated conduction slowing in clinically unaffected nerve segments. These neurophysiological changes correlated with severity of renal impairment, and the clinical symptoms and nerve conduction parameters were noted to improve rapidly following renal transplantation, often within days of surgery.17–19 The rapidity of these changes suggests that toxin-mediated blockade of neural transmission has an important role in the neurological dysfunction associated with CKD.

Several studies have postulated that ‘middle molecules’ (molecular weight 300–12,000 Da)20 are the toxins that underlie the development of neurological dysfunction in CKD, yet little evidence exists that such substances are actually neurotoxic.21 Five criteria have been proposed that should be met for a substance to be considered as a uremic neurotoxin (Box 2).22,23

On the basis of this framework, studies of uremic neuropathy have applied the rationale that biochemical alterations in CKD will result in dysfunction of the axonal membrane that can be reversed with hemodialysis.24 In support of this idea, nerve excitability studies undertaken over the course of a dialysis session have demonstrated correlations between axonal membrane dysfunction and serum potassium levels (Figure 2), suggesting that hyperkalemia, driven by reduced excretion of potassium and consequent elevations in total body potassium, contributes to the development of neuropathy in CKD.25,26 Studies of muscle strength in patients with CKD and healthy controls have also suggested that impaired potassium regulation underlies muscle fatigue, thereby contributing to exercise limitation.27,28 Further studies will be required to establish a causal relationship between hyperkalemia and neurological disease in CKD, although potassium does satisfy all the proposed criteria for a uremic neurotoxin (Box 2), in addition to having a pivotal role in the maintenance of resting membrane potential and neuronal homeostasis.22

Cognitive impairment

Cognitive dysfunction increases in prevalence with CKD severity,29–31 potentially affecting up to 80% of patients.14,32 Cognitive impairment in CKD not only increases the risk of mortality, but also has major implications for informed consent in relation to dialysis initiation and maintenance, and, ultimately, renal transplantation.14,33–35

Acute cognitive impairment

In addition to chronic cognitive dysfunction and dementia, acute disturbances of cognition are prevalent in CKD. In the early days of dialysis, these acute disturbances frequently took the form of the ‘dialysis disequilibrium syndrome’,36 a specific clinical entity characterized by symptoms such as headache, nausea, vomiting, tremor and confusion that commenced during or soon after a hemodialysis session. This syndrome was related to rapid shifts in urea levels, which induced cerebral edema.
With modern dialysis regimens that incorporate smaller dialysate volumes and more-frequent dialysis sessions, this syndrome is now an uncommon complication.

Despite advances in dialysis, acute disturbances in cognitive function still occur in patients with CKD. These disturbances typically relate to metabolic abnormalities that complicate the uremic state, including electrolyte disturbances (for example, hypercalcemia, hypophosphatemia and hyponatremia), acute fluid shifts during dialysis, which lead to cerebral hypoperfusion, and malignant hypertension, which causes encephalopathy.

Generalized or focal seizures can develop in the context of acute metabolic instability in patients with CKD. When selecting an appropriate anticonvulsant, an important consideration is that medications showing low protein binding and high solubility in water are easily removed by hemodialysis, and might, therefore, require supplemental dosing following a dialysis session. Medications with these properties include the newer anticonvulsants, such as gabapentin, topiramate and levetiracetam. Older medications, such as phenytoin, sodium valproate and carbamazepine, are highly protein bound, with only a small proportion of the total drug persisting in the free, active state. Consequently, these latter medications have tended to be preferred for the treatment of seizures that complicate end-stage kidney disease. Post-dialysis reductions in phenytoin levels have been reported, although the need for supplemental dosing is largely determined by free drug levels. Even small reductions in the plasma protein concentration, which occur in patients with CKD as a result of albuminuria, can lead to a marked increase in the amount of active drug, thereby predisposing the patient to drug toxicity.

The potential for rapid variations in cognitive function was emphasized by a study of patients with CKD who underwent cognitive testing at multiple time points before and after a single dialysis session. In these patients, global cognitive function varied markedly, with the greatest impairments being noted during the dialysis session, particularly with regard to memory, executive functioning and verbal fluency. These results suggested that clinical review of dialysis patients and the communication of important information, such as obtaining informed consent or discussion of treatment changes, should be undertaken outside dialysis sessions.

Chronic cognitive impairment and dementia

Kidney failure represents an independent risk factor for progressive cognitive impairment and dementia. Moderate renal impairment that does not require dialysis is also associated with a significantly increased risk of dementia, independent of other vascular risk factors. Cognitive tests demonstrate objective evidence of moderate to severe cognitive impairment in 70% of patients with CKD, with dysfunction most commonly noted in the domains of memory and executive function. Others have noted marked abnormalities of executive function in CKD, which were interpreted as evidence of disruption in frontal–subcortical circuits, consistent with a subcortical pattern of cognitive dysfunction. Preferential alteration in memory function suggestive of an Alzheimer-type dementia can occur in CKD, but the cognitive changes in this condition more typically indicate a combination of Alzheimer disease and vascular dementia.

Pathophysiology of cognitive impairment

The preponderance of vascular dementia in CKD was initially taken as evidence that cognitive impairment was secondary to the increased prevalence of vascular risk factors in these patients. MRI studies have demonstrated a high incidence of clinically silent cerebrovascular disease.
in patients with CKD, which seems to be related to the degree of renal impairment. The importance of silent cerebrovascular disease is underscored by studies of healthy individuals that demonstrated an association between cognitive impairment and silent brain infarction, which was most commonly attributable to subcortical lacunar infarcts. MRI studies have shown that clinically silent white matter disease is present in 50% of patients with CKD, compared with 10% in the general population. These changes can take the form of isolated lacunar infarction or confluent white matter hyperintensity. Risk factors for white matter disease in CKD include advanced age, hypertension and smoking. Patients in whom vascular nephropathy is the cause of CKD are at a particularly high risk of white matter disease, suggesting that white matter lesions are ischemic in origin. In further support of this argument, silent brain infarction has been shown to be an independent risk factor for future cerebral and vascular morbidity in patients on dialysis.

Although vascular disease remains a major cause of morbidity in CKD, studies to date have failed to establish a direct link between traditional vascular risk factors, such as diabetes and hypertension, and cognitive dysfunction in CKD. Moreover, although mild renal impairment is an independent risk factor for ischemic stroke, a connection between acute stroke and cognitive impairment in CKD has not been established. Taken together, these studies suggest that the high prevalence of cognitive dysfunction in patients with CKD is mediated by factors that are specific to the disease. Accordingly, a possible role has been suggested for novel vascular risk factors that are of heightened relevance to CKD patients; in particular, the elevated levels of inflammatory mediators that have been noted in this group. This finding is of particular relevance given the previously identified link in the general population between inflammatory markers and all-cause dementia.

As regards nonvascular risk factors, studies conducted in the 1970s implicated aluminum, which is contained in phosphorus binders and dialysate water, as the cause of ‘dialysis dementia’. This hypothesis was supported by the discovery of elevated aluminum levels in cerebral gray matter in patients with CKD. Modern techniques of water purification and the use of non-aluminum phosphorus binders have, however, made aluminum intoxication a rare complication of CKD. A more recent focus relates to the potential roles of secondary hyperparathyroidism and anemia as risk factors for cognitive impairment in the CKD population. Animal studies have identified parathyroid

### Table 1 | Neurological disorders in patients with CKD

| Neurological disorder | Prevalence | Clinical features | Management |
|-----------------------|------------|------------------|------------|
| Cognitive dysfunction | 30–40% of patients on dialysis | Impairments in memory and executive function | Most effective: renal transplantation<br>Other option: erythropoietin |
| Restless legs syndrome | 15–20% of patients with CKD | Subjective urge to move the legs, worse nocturnally; symptoms exacerbated by inactivity and relieved by movement | Most effective: dopaminergic agonists; levodopa<br>Other option: advice regarding sleep hygiene |
| Length-dependent uremic neuropathy | 90% of patients with CKD | Sensory loss, weakness and wasting, maximal distally; absence of ankle jerks; lower limbs more severely affected than upper limbs | Most effective: transplantation, adequate dialysis (increase frequency or use high-flux dialysis); neuropathic pain therapy<br>Other options: vitamin supplementation; strict potassium restriction; erythropoietin; exercise program |
| Autonomic neuropathy | ~60% of patients with CKD | Impotence; postural hypotension; cardiac arrhythmia; symptomatic intradialytic hypotension | Most effective: transplantation; adequate dialysis; sildenafil to treat impotence<br>Other option: midodrine to treat intradialytic hypotension |
| Carpal tunnel syndrome | 5–30% of patients with CKD | Hand paresthesia and numbness; weak thumb abduction | Most effective: splinting; local steroid injection; surgical decompression |
| Ischemic monomelic neuropathy | Rare in CKD | Diffuse weakness and sensory loss distal to an arteriovenous fistula | Immediate fistula banding or ligation |
| Uremic myopathy | 50% of patients with CKD | Proximal weakness of the lower limbs | Most effective: adequate dialysis; exercise program; adequate nutrition<br>Other options: erythropoietin; l-carnitine |

Abbreviation: CKD, chronic kidney disease.

### Box 2 | Proposed criteria for a uremic neurotoxin

- Must be an identifiable chemical
- Should be elevated in the blood of patients with uremia
- A direct positive relationship should exist between blood level and neurological dysfunction
- Should cause neurological dysfunction in experimental animals at appropriate blood levels
- Removal from the blood should abolish the neurological dysfunction
Restless legs syndrome

Patients with RLS complain of a subjective urge to move their legs, frequently accompanied by dyesthesia. The symptoms are aggravated by periods of relative inactivity, are relieved by movement, and have a characteristic nocturnal exacerbation that causes considerable difficulty in initiating sleep. A family history of RLS, with a dominant pattern of inheritance, is present in 40% of patients with this condition.66 RLS is present in ~15–20% of patients on dialysis, and is associated with insomnia and reduced quality of life.67 In contrast to this high prevalence, the occurrence of small-fiber neuropathy, which has been described in other metabolic disorders68 and can cause symptoms that are similar to RLS, is an uncommon entity in CKD.69

RLS can either be idiopathic or secondary to conditions such as CKD, iron deficiency, pregnancy or peripheral neuropathy.70,71 The symptoms are more severe in dialysis patients with RLS than in individuals with the idiopathic form, and periodic limb movements are also more frequent in patients on dialysis.72 RLS tends to be exacerbated by caffeine, alcohol, and medications that include dopamine antagonists, lithium, selective serotonin reuptake inhibitors, and tricyclic antidepressants.73 The neurological examination is typically normal in RLS, but on polysomnography 80% of patients will manifest an increased rate of periodic limb movements.66

A disturbance of dopaminergic transmission has been postulated to underlie the development of idiopathic RLS,74,75 but the increased incidence in CKD might reflect hyperphosphatemia76 or iron deficiency.77 From a therapeutic perspective, assessment of sleep hygiene and lifestyle factors is an essential part of the management of RLS.73 Anemia contributes to the development of RLS in the dialysis population, and treatment with intravenous iron reduces the severity of symptoms.75,78 Renal transplantation leads to improvements in RLS symptoms and a reduction in insomnia.79,80 Dopaminergic agonists and levodopa are considered to be first-line pharmacological treatments for RLS, although long-term treatment with the latter agent is associated with daytime augmentation of symptoms.81

Effects of renal transplantation

Clear evidence now exists that cognitive function improves following renal transplantation. In a recent study of patients with CKD, improvements in cognition in relation to baseline values were demonstrated 6 months after transplantation.80 Prominent changes were evident with regard to memory, with minor improvements also noted in the domains of concentration and psychomotor function. Other groups have demonstrated improvements in both neuropsychological tests, such as the Mini-Mental State Examination, and neurophysiological markers of cognitive function, as measured using evoked potential latencies and EEG rhythms.81–85

hormone as neurotoxic, and the increased brain calcium content, driven by elevated parathyroid hormone levels, in patients with CKD has been postulated to interfere with neurotransmission in the CNS.85,86 Anemia has also been identified as a risk factor for cognitive impairment in CKD, and correction of anemia with erythropoietin treatment has been shown to improve measures of cognition.14,61

Figure 2 | Nerve excitability over the course of a dialysis session. Nerve excitability recordings obtained from the abductor pollicis brevis muscle following median nerve stimulation at the wrist in a single representative patient with uremic neuropathy. Blue lines denote recordings before dialysis and red lines denote recordings 1 hour after dialysis. 95% CIs for normal controls are indicated by dotted lines. The patient was hyperkalemic before dialysis (serum potassium 5.7 mmol/l; normal range 3.6–5.1 mmol/l) and normokalemic after dialysis. a | Threshold electrotonus curves, which assess nodal and internodal ion channel function, demonstrate a ‘fanning-in’ appearance (arrows) in pre-dialysis recordings, indicating membrane depolarization. b | Recovery cycle. The recovery cycle shows an upward shift—another feature of membrane depolarization—before dialysis. Post-dialysis recordings demonstrate a return to the normal range.
Uremic neuropathy

The development of uremic neuropathy is exceedingly common in CKD, with prevalence rates of 60–90% in the dialysis population. The development of clinically relevant neuropathy tends to be a late complication that is typically limited to patients with end-stage kidney disease (stage 5 CKD; Box 1). Uremic neuropathy presents as length-dependent polyneuropathy, in which the earliest clinical features reflect involvement of large, myelinated sensory fibers, causing paresthesia and numbness. Clinical examination demonstrates distal sensory loss in the lower limbs and a reduction in ankle deep tendon reflexes. With more-severe disease, motor involvement occurs, leading to weakness and muscle atrophy, again most prominent distally (Figure 3).

In patients with prominent motor involvement or rapid clinical progression over days to weeks, alternative diagnoses—in particular, inflammatory demyelinating neuropathy—need to be considered. Both acute and chronic inflammatory demyelinating polyneuropathy have been described in patients with CKD, and in most of these patients the underlying renal disorder is either membranous or focal sclerosing glomerulonephritis.

The worldwide health burden imposed by diabetes, the commonest cause of CKD, is likely to add to the prevalence and severity of neuropathic symptoms in patients with CKD, given that diabetes on its own causes neuropathy in >50% of patients. Patients with CKD and diabetes develop length-dependent neuropathy of greater severity than do nondiabetic CKD patients. In addition to length-dependent neuropathy, diabetic CKD patients can also develop a rapidly progressive neuropathy of an axonal or demyelinating type. These patients might benefit from switching from conventional to high-flux dialysis, which facilitates the removal of the advanced glycation end products that have been implicated in the development of both diabetic neuropathy and nephropathy.

Diagnosis

The first step in the diagnosis of uremic neuropathy is to exclude other causes of neuropathy, especially glucose dysmetabolism, which frequently accompanies CKD. In those patients who have rapidly progressive weakness, serological testing should be undertaken to exclude vasculitic neuropathy. Nerve conduction studies (NCS) remain the gold standard in the diagnosis of uremic neuropathy. In length-dependent uremic neuropathy, NCS demonstrate features of a generalized neuropathy of the axonal type, with reductions in sensory amplitudes, and, to a lesser extent, motor amplitudes, and relative preservation of conduction velocities. Of the various nerve conduction parameters, sural sensory amplitude is the most sensitive indicator of uremic neuropathy, and is reduced in 50% of cases. In contrast to axonal length-dependent uremic neuropathy, CKD patients with demyelinating neuropathies manifest prominent slowing of nerve conduction, often with preserved sensory and motor amplitudes in the early stages of the disease.

Management

Renal transplantation remains the only cure for uremic neuropathy and must be considered in any patient with progressive neuropathy. Rapidly progressive neuropathy is an accepted indication for patients to be triaged to urgent, nonmatched transplantation lists. Following transplantation, clinical recovery typically occurs over a period of 3–6 months, although some patients continue to experience improvement for up to 2 years. In CKD patients with diabetes, combined renal and pancreatic transplantation produces considerable clinical and neurophysiological improvement. Crucially, patients with severe neuropathy can fail to recover, emphasizing the need for preventive strategies.

Standard three times per week dialysis regimens generally halt the progression of neuropathy, but such regimens rarely result in substantial clinical improvement. Progressive neuropathy, however, is both an indication for the commencement of dialysis therapy and an important indicator of insufficient dialysis. Patients with neuropathy must, therefore, meet the current guidelines of dialysis adequacy. In some cases, alterations to the dialysis regimen, such as a change to daily dialysis or high-flux dialysis (a form of dialysis that allows improved removal of toxins and fluids), will prevent clinical deterioration.

In CKD patients with demyelinating neuropathy, standard immunomodulatory treatments such as intravenous immunoglobulin have been used with some success, although the potential benefits must be balanced against the small but well-documented risk of nephrotoxicity. This issue is particularly pertinent to patients who have some residual kidney function, and in whom nephrotoxic complications could precipitate the need for dialysis treatment. Accordingly, plasma exchange and steroid treatment should be considered as potential alternatives to intravenous immunoglobulin. Patients with painful neuropathy benefit from treatment with...
tricyclic antidepressants, such as amitriptyline, or with anticonvulsant medications, such as sodium valproate or gabapentin. Vitamin supplementation with pyridoxine and methylcobalamin has also been shown to improve neuropathic pain in CKD, while exercise training programs might improve muscle strength, cardiorespiratory function and work capacity. The potential role of potassium in the development of uremic neuropathy has raised the possibility that strict dietary restriction of potassium could be beneficial. This strategy is likely to be of importance not only for patients on dialysis, in whom maintenance of serum potassium within normal limits between periods of dialysis might prevent neuropathy progression, but also for patients with early-stage CKD, in whom such a strategy could potentially help to prevent the development of neuropathy.

**Autonomic neuropathy**

Autonomic dysfunction is a common and potentially life-threatening complication of CKD, and can occur in the absence of length-dependent uremic neuropathy. Cardiovascular autonomic dysfunction in CKD is associated with an increased risk of cardiac arrhythmia and sudden cardiac death. Assessment of autonomic function has demonstrated abnormalities in 60% of patients with CKD, particularly relating to measures of parasympathetic function, such as heart rate response to deep breathing, induced hypotension, and the Valsalva maneuver.

Impotence remains the most common symptom of autonomic dysfunction in CKD, and it develops in the majority of male patients. Other common clinical features include bladder and bowel dysfunction, impaired sweating, and orthostatic intolerance. Arterial calcification might contribute to autonomic symptoms in CKD by reducing the sensitivity of baroreceptors in the arterial wall that mediate the short-term regulation of blood pressure. In addition to a potential role in sudden cardiac death, reduced baroreflex sensitivity can also contribute to intradialytic hypotension, a condition occurring during dialysis that is characterized by an abrupt reduction in blood pressure without a compensatory increase in heart rate. Intradialytic hypotension is an independent risk factor for mortality in CKD, and its symptoms include dizziness, blurred vision, cramps, nausea and vomiting.

Renal transplantation leads to considerable improvement in autonomic function, whereas dialysis treatments do not result in a substantial change. Erectile dysfunction responds to treatment with sildenafil, and for patients with intradialytic hypotension, the oral a1-adrenoceptor agonist midodrine, administered 15–30 minutes before a dialysis session, may be beneficial.

**Other neuropathies**

**Carpal tunnel syndrome**

Carpal tunnel syndrome (CTS) is common in CKD, with a prevalence of 26% in patients who have been on dialysis for more than 4 years. The high prevalence of CTS in CKD has been attributed to various factors. The presence of arteriovenous fistulas, for example, can predispose an individual to nerve ischemia by causing a steal syndrome. Alternatively, β2-microglobulin amyloidosis, a complication of long-term hemodialysis that results from poor clearance of β2-microglobulin by standard dialysis membranes, can lead to localized deposition of amyloid that is confined to soft tissues.

CTS typically presents with sensory symptoms—in particular, paresthesia, numbness and pain—that can increase in severity during a dialysis session. In the case of longstanding disease, motor involvement can occur, leading to weakness and wasting of distal muscles innervated by the median nerve (for example, the abductor pollicis brevis). NCS demonstrate slowing of distal median nerve conduction, with normal sensory and motor amplitudes in early CTS, and reductions in amplitudes, reflecting axonal loss, in more-advanced CTS.

Treatments for CTS range from splinting or local corticosteroid injections for mild disease (characterized by mild symptoms and normal sensory and motor amplitudes on NCS) to surgical decompression in cases where symptoms are either refractory to conservative treatments or where NCS have demonstrated changes indicative of axonal loss. Surgical decompression by means of an extended carpal tunnel release procedure confers marked clinical improvement, although an inferior outcome has been reported in patients who had fixed motor or sensory deficits before surgery. For patients on long-term dialysis treatment and in whom amyloid deposition is a probable etiology for CTS, biopsy specimens should be obtained at the time of surgery to assess whether amyloid deposits are present in the flexor retinaculum.

**Ischemic monomelic neuropathy**

Patients who have undergone recent insertion of a forearm arteriovenous fistula can, within hours of fistula insertion, develop acute weakness and sensory dysfunction in a pattern suggesting involvement of multiple peripheral nerves. This rare complication of forearm fistula insertion is termed ischemic monomelic neuropathy (IMM), and it results from shunting of blood away from the distal regions of the arm. This process leads to acute peripheral nerve ischemia, which affects the distal portions of multiple upper limb nerves simultaneously, typically in the absence of notable soft tissue injury. IMM has been described almost exclusively in patients with diabetes or severe peripheral vascular disease. A subacute vascular steal syndrome that can occur weeks to months following fistula insertion has also been described. In contrast to IMM, patients with vascular steal syndrome develop marked soft tissue injury that can cause ischemic ulceration and even gangrene.

Treatment for IMM and vascular steal syndrome consists of emergency fistula ligation or banding.

**Uremic myopathy**

The development of a myopathy in CKD causes proximal muscle weakness and wasting, predominantly in the
muscles of the lower limbs. Uremic myopathy typically develops with glomerular filtration rates of <25 ml/min, and has been associated with fatigability and reduced exercise capacity.\textsuperscript{15,128} Electromyography and creatine kinase levels are generally normal, and the diagnosis is, therefore, made largely on clinical grounds. Muscle biopsy tends to demonstrate nonspecific features, including type II fiber atrophy with internalized nuclei and fiber splitting.\textsuperscript{127} The precise mechanisms underlying the development of uremic myopathy remain unclear, but the relatively high prevalence of myopathy among diabetic CKD patients has led to the suggestion of a role for insulin resistance.\textsuperscript{15,128} Other possible etiologies include hyperparathyroidism, metabolic bone disease with vitamin D deficiency, impaired potassium regulation, accumulation of uremic toxins, and carnitine deficiency, which can lead to mitochondrial dysfunction.\textsuperscript{15,28,129–132} Malnutrition has also been postulated to play a part, with reductions in RNA content and amino acid levels noted in muscle biopsy samples obtained from patients with CKD.\textsuperscript{133,134}

Treatments that might improve exercise tolerance and muscle function in patients with CKD include optimization of dialysis efficacy, management of hyperparathyroidism and vitamin D deficiency, nutritional supplementation, and use of erythropoietin to correct anemia.\textsuperscript{135,136} Exercise programs provide considerable benefits, such as an increase in muscle bulk and improvements in work performance.\textsuperscript{137} Trials of L-carnitine supplementation, on the other hand, have produced mixed results, with some studies demonstrating improvements in exercise tolerance and others indicating no benefit.\textsuperscript{138–140}

Conclusions
Neurological complications represent a major cause of disability and markedly impair quality of life in patients with CKD. Neurologists play a critical part in the diagnosis and therapeutic management of these complications. Cognitive impairment in patients with CKD, which can be present even in moderate renal insufficiency, is likely to improve with renal transplantation. The alteration in axonal membrane potential that develops in uremic neuropathy seems to be driven by chronic hyperkalemia. Future studies could shed further light on the beneficial effects of strict potassium control on neuropathy in CKD, and on neuromuscular function more generally. Autonomic dysfunction, which is highly prevalent in CKD, is associated with vascular calcification, cardiac arrhythmia and sudden cardiac death. For CKD patients with myopathy, exercise programs, adequate nutritional intake, and treatment with erythropoietin to correct anemia remain the mainstays of therapy to improve exercise tolerance and neuromuscular function.

Review criteria
OVID MEDLINE was searched for papers published between January 1966 and April 2009, using the terms “chronic kidney disease”, “dialysis” and “end-stage kidney disease”. Each keyword was then combined with the following terms: “cognitive impairment”, “neuropathy”, “myopathy”, “autonomic neuropathy”, “restless legs syndrome” and “carpal tunnel syndrome”. Searches were restricted to articles in English. Further articles were identified from reference lists and review articles. The final reference list was generated on the basis of originality and relevance to the topics covered in the Review.

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Acknowledgments
A. V. Krishnan was supported by a Career Development Award (Grant number 569680) of the National Health and Medical Research Council. Grant funding from the Brain Foundation and Pfizer Neuroscience Grants Scheme is gratefully acknowledged.

Charles P. Vega, University of California, Irvine, CA is the author of and is solely responsible for the content of the learning objectives, questions and answers of this review. The author received Brain Foundation and Pfizer Neuroscience Grants (Grant number 568680) of the National Health and Medical Research Council. Grant funding from the Brain Foundation and Pfizer Neuroscience Grants Scheme is gratefully acknowledged.

A. S. Berman is a recipient of the National Health and Medical Research Council. Grant funding from the Brain Foundation and Pfizer Neuroscience Grants Scheme is gratefully acknowledged.

James P. A. Wilson, University of California, Irvine, CA is the author of and is solely responsible for the content of the learning objectives, questions and answers of this review. The author received Brain Foundation and Pfizer Neuroscience Grants (Grant number 568680) of the National Health and Medical Research Council. Grant funding from the Brain Foundation and Pfizer Neuroscience Grants Scheme is gratefully acknowledged.