Neuropathy and Other Neurological Problems in Chronic Kidney Disease

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Ria Arnold and Arun V. Krishnan

Before You Start: Facts You Need to Know

- Neurological complications are highly prevalent in CKD and contribute substantially to patient morbidity and mortality risk.
- The uremic state can potentially affect all levels of the nervous system, from central nervous system disorders, such as encephalopathy and cognitive dysfunction, to peripheral disorders such as myopathy and autonomic and peripheral neuropathies.
- Neurological complications often become clinically apparent with severe kidney disease; however, detection and management of these conditions in earlier stages of CKD may reduce their impact at later stages.

26.1 Neuropathy in CKD

Neurological complications are highly prevalent in patients with CKD. The systemic nature of uraemia causes a variety of neurological disorders potentially affecting all levels of the nervous system [1] (Fig. 26.1). These may manifest as central nervous system disorders, such as encephalopathy and cognitive dysfunction, to peripheral disorders such as myopathy and autonomic and peripheral neuropathies (Table 26.1). It is evident that these conditions have significant impacts on patient morbidity and mortality [2, 3]. While quality of life is profoundly affected by these conditions, increased mortality is also a significant concern, particularly where there is severe encephalopathy causing coma or advanced neuropathy, which may lead to skin ulceration and even gangrene [4]. Furthermore, less common causes of CKD may also affect the central and/or peripheral nervous system independent of uraemia such as amyloidosis, systemic lupus erythematosus, hepatic failure, Wilson's disease and Fabry's disease [5]. Despite this, there are currently no clinical guidelines for the management of neurological complications in CKD and only brief mentions of this topic in K/DOQI Clinical Practice Guidelines (Box 26.1). Given that most neurological complications manifest with an eGFR of less than 20 mL/min, their prevalence is only clearly documented in stage 5 CKD and dialysis populations. However, the association between declining kidney function and severity of neurological complications [4] suggests that

R. Arnold, BS
Department of Neurological Sciences,
Prince of Wales Hospital,
High Street, Randwick, Sydney, NSW 2031,
Australia
e-mail: r.arnold@neura.edu.au,
ria.arnold@unsw.edu.au

A.V. Krishnan, MBBS, PhD, FRACP (✉)
Department of Neurology, Prince of Wales Hospital,
High Street, Randwick, Sydney, NSW 2031,
Australia
e-mail: arun.krishnan@unsw.edu.au

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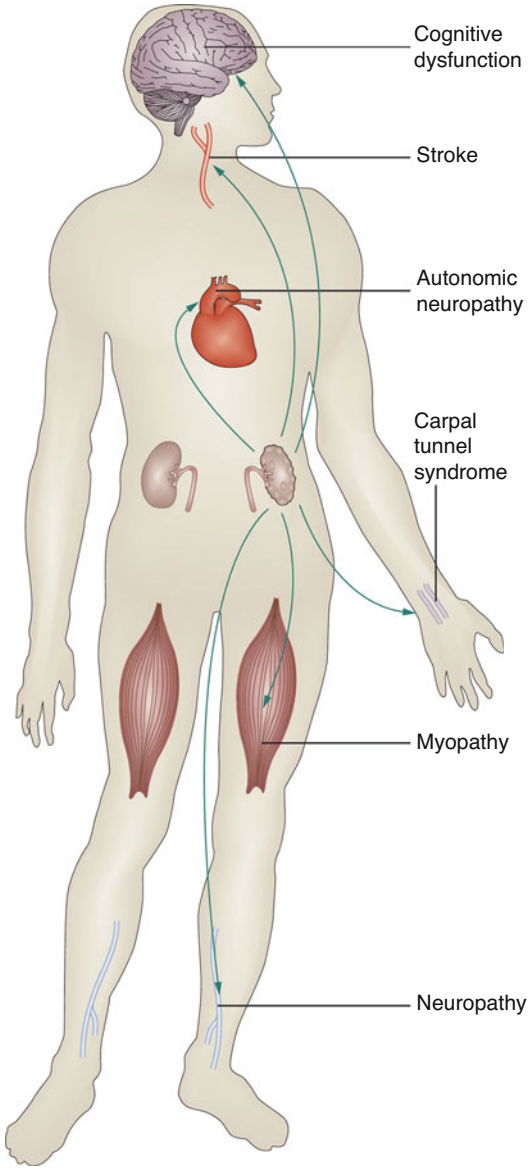

Fig. 26.1 The spectrum of neurological complications in chronic kidney disease (Reprinted from Krishnan and Kiernan [1])

pathological changes occur in earlier stages of CKD. As such, detection and management of these conditions in earlier stages of CKD may provide a window of opportunity to reduce their impact at later stages.

26.1.1 Peripheral Neuropathy

26.1.1.1 Definition

The most common neurological complication of CKD is peripheral neuropathy, also known as uremic neuropathy, which affects 60–90 % of dialysis patients [1]. The onset and severity of uremic neuropathy closely relates to the severity of kidney dysfunction with most cases becoming clinically evident at glomerular filtration rates of <12 mL/min [7]. The prevalence of uremic neuropathy in earlier stages of CKD has not been systemically investigated. However, the increasing incidence of diabetic nephropathy introduces a highly susceptible patient cohort that may have pre-existing neuropathy and are thus likely to have neuropathy of greater severity [2, 8]. Patients typically experience symptoms such as pain, paraesthesia and numbness, which may become functionally disabling [9]. Furthermore, this disorder negatively impacts on quality of life, increases risk of lower extremity amputation and thereby increases morbidity and mortality risk, especially for those with diabetic nephropathy [2, 8].

26.1.1.2 Clinical Presentation

Peripheral neuropathy typically manifests as a slowly progressive, symmetrical, length-dependent neuropathy of insidious onset. Given the length-dependent nature of peripheral neuropathy, there is preferential involvement of distal nerves and more severe involvement of the lower limbs than upper limbs [9]. As such, clinical examination in early stages reveals symptoms and signs confined to the lower limbs, including distal sensory loss to pinprick and vibration and reduced or absent ankle deep tendon reflexes [2, 9]. With more severe disease, sensory involvement progresses proximally and upper limb involvement may occur in a 'stocking-and-glove' distribution. In advanced cases, motor nerve involvement can develop resulting in muscle atrophy and weakness, which is again most prominent distally [9] (Fig. 26.2). Assessment of power in intrinsic foot muscles, such as extension

Table 26.1 Neurological disorders in patients with CKD

Neurological disorder	Prevalence	Clinical features	Management
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 Other options: vitamin supplementation; potassium restriction; erythropoietin; exercise programmes
Autonomic neuropathy	50–60 % of patients with CKD	Impotence; postural hypotension; cardiac arrhythmia; symptomatic intradialytic hypotension	Most effective: transplantation; adequate dialysis; sildenafil to treat impotence Other option: midodrine to treat intradialytic hypotension
Cognitive dysfunction	30–40 % of patients on dialysis	Impairments in memory and executive function	Most effective: renal transplantation Other option: erythropoietin
Encephalopathy	–	Sensorial clouding, apathy, irritability; confusion, disorientation, coma Motor disturbances, tremor, asterixis, myoclonus	Dialysis Seizure treatment: phenytoin, sodium valproate or carbamazepine
Carpal tunnel syndrome	5–30 % of patients with CKD	Hand paraesthesia and numbness; weak thumb abduction	Most effective: splinting; local steroid injection; surgical decompression
Myopathy	~50 % of patients with CKD	Proximal weakness of the lower limbs	Most effective: adequate dialysis; exercise programme; adequate nutrition Other options: erythropoietin; l-carnitine

Source: Adapted from Krishnan and Kiernan [1]
Abbreviation: *CKD* chronic kidney disease

Box 26.1. Relevant Guidelines

1. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Part 6. Association of level of GFR with complications in adults. Am J Kidney Dis. 2002;39:S111–69 [4]
2. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1–150. Available from: http://www.kdigo.org/clinical_practice_guidelines/CKD.php [6]

of the big toe, may provide clues to early motor involvement. While damage to large motor and sensory fibres is typical of uremic neuropathy, small fibre neuropathy may also occur. In diabetic patients, small fibre symptoms may dominate with patients experiencing severe burning and shooting pain and altered temperature and pain perception [2].

26.1.1.3 Diagnostic Investigations

Clinical diagnosis of uremic neuropathy requires careful exclusion of alternate causes of neuropathy, including glucose dysmetabolism and connective tissue disease. The presence of glucose dysmetabolism is a critical factor given the likelihood of pre-existing neuropathy and greater severity of neuropathy seen in diabetic CKD

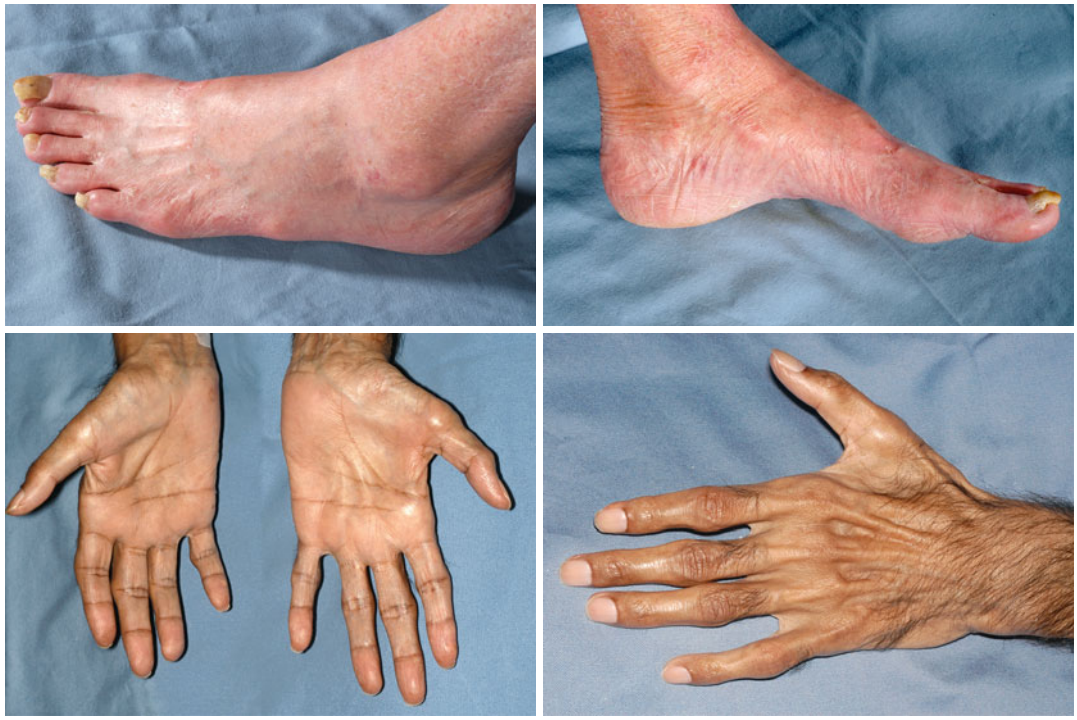

Fig. 26.2 Wasting of the intrinsic distal muscles in two patients with uremic neuropathy. In addition to weakness, the patients complained of numbness and had impaired joint position sense (Reprinted from Krishnan [9])

patients. Connective tissue disorders may be associated with a rapidly progressive neuropathy due to peripheral nerve vasculitis. Other causes of rapidly progressive neuropathy in CKD include inflammatory demyelinating neuropathies, such as chronic inflammatory demyelinating polyneuropathy, which have been described in the context of CKD due to glomerulonephritis [1]. Unlike typical length-dependent uremic neuropathy which presents with sensory features, inflammatory neuropathies are often characterised by marked motor involvement even at the onset of the disease. Demyelinating neuropathies require early recognition, as prompt treatment with immunotherapy may lead to clinical improvement [1].

Nerve conduction studies are the gold standard for the diagnosis of neuropathy. Nerve conduction studies in CKD patients with neuropathy reveal reduced sensory amplitudes and to a lesser extent motor amplitudes with relative preservation of motor and sensory conduction velocities, findings consistent with a generalised neuropathy of the axonal type [9] (Fig. 26.3). In contrast to axonal neuropathies, demyelinating neuropathies demonstrate significant reductions in nerve conduction velocities, often with relatively preserved motor and sensory amplitudes.

26.1.1.4 Management

The presence and progression of severe neuropathy may be an important indicator of the need to initiate dialysis [4]. Routine dialysis treatment may halt the progression of neuropathy but rarely results in clinical improvement. Recent studies suggest that enhanced dialysis strategies such as high flux dialysis and hemodiafiltration may result in improved outcomes. Renal transplantation is the only treatment recognised to enable clinical improvement in peripheral neuropathy. However, in advanced cases of neuropathy, clinical recovery may not occur, emphasising the need for prevention [1]. Recent studies have demonstrated that hyperkalaemia has a detrimental effect

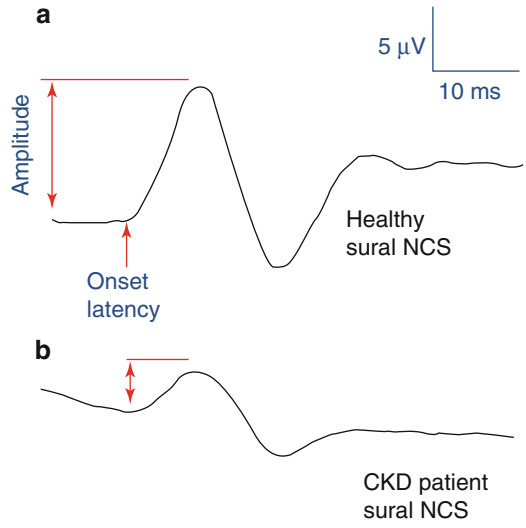

Fig. 26.3 Sensory nerve conduction results of the sural nerve, a lower limb sensory nerve, for a healthy control subject (**a**) and a chronic kidney disease patient (**b**). Results in the chronic kidney disease patient demonstrate a reduction in amplitude of the sensory nerve amplitude consistent with a sensory neuropathy

on nerve function in CKD and emphasise the importance of achieving normokalaemia in CKD patients [1, 7]. Additionally, glycemic control remains an important preventative strategy in patients with diabetic CKD. Attention to foot care is an integral part of managing neuropathy in both CKD and diabetes [8]. Reducing the risk of foot ulcers and infective complications requires assessment of predisposing factors such as ill-fitting shoes which may require the involvement of a podiatrist [8, 9]. Exercise programmes may indirectly prove beneficial to neuropathy by improving muscle strength, cardiorespiratory function and glycemic control [10].

Painful neuropathy may be managed with use of membrane-stabilising neuropathic pain treatments, including a range of tricyclic antidepressants (e.g. amitriptyline) and anticonvulsants (e.g. sodium valproate, carbamazepine, pregabalin and gabapentin) [2]. However, these medications have a constellation of potential side effects, and anticonvulsants typically require dosing restrictions for patients with CKD [2]. Tricyclic antidepressants are often used as first-line treatment for painful neuropathic symptoms due to ease of once-daily dosing which may help improve compliance [1, 2]. However, treatment with these agents may be poorly tolerated by older patients, and these agents are therefore used with caution in patients with cardiac arrhythmias, congestive heart failure, orthostatic hypotension and urinary retention [2]. Alternative treatments include anticonvulsant medications such as pregabalin or gabapentin, although both have dosing restrictions in patients according to creatinine clearance [1, 2]. Symptoms of neuropathic pain in CKD may also be reduced by vitamin supplementation with pyridoxine and methylcobalamin [1].

Demyelinating neuropathies are typically treated with intravenous immunoglobulin; however, the risk of nephrotoxicity with this treatment must be carefully considered in patients who have some degree of residual kidney function [1]. Potential alternative treatments include plasma exchange or steroid treatment.

26.1.2 Autonomic Neuropathy

26.1.2.1 Definition

Autonomic dysfunction is a highly prevalent complication of CKD with potentially life-threatening consequences such as cardiac arrhythmia, silent myocardial ischaemia and sudden cardiac death [1, 2]. Autonomic dysfunction occurs in up to 60 % of patients with stage 5 CKD [4]. Studies of diabetic CKD patients who have CKD of moderate severity have demonstrated prevalence rates of 50 %, underscoring the possibility that autonomic impairment may potentially occur prior to the initiation of renal replacement therapy [4].

26.1.2.2 Clinical Presentation

The most common symptom of autonomic neuropathy is impotence which develops in the majority of male patients [1]. Other clinical manifestations may include bladder and bowel dysfunction and evidence of altered sudomotor function manifesting as dry skin and impaired sweating. Cardiovascular autonomic dysfunction may present with orthostatic intolerance, reduced

exercise tolerance, palpitations and loss of consciousness due to cardiac arrhythmia.

26.1.2.3 Diagnostic Investigations

Clinical assessment of autonomic function may be undertaken using a variety of techniques such as assessment of cardiac and pupillary reflexes, sweating and blood pressure control [9]. Assessment of cardiac autonomic neuropathy requires a battery of tests including heart rate variability, Valsalva manoeuvre and changes in heart rate with standing [2].

26.1.2.4 Management

As has been previously discussed in the case of peripheral neuropathy, renal transplantation improves autonomic function, while dialysis treatment rarely results in substantial change [1]. With the commencement of dialysis, intradialytic hypotension may become problematic for patients with autonomic neuropathy. In these cases treatment with midodrine administered 15–30 min prior to dialysis may improve symptoms. Erectile dysfunction responds to treatment with phosphodiesterase type 5 inhibitors such as sildenafil, which is well tolerated [1]. The optimal management for cardiac autonomic neuropathy remains unclear. While some evidence has suggested that angiotensin-converting enzyme inhibitors may be helpful in reducing heart rate variability, other evidence has demonstrated either no benefit or a potentially deleterious effect of these medications [2]. The use of beta blockers in CKD patients has been limited due to concerns for potentially higher rates of adverse effects, including hyperkalaemia and glycaemic abnormalities [2]. However, recent studies have shown that beta blockers may provide cardiovascular protection in patients with advanced CKD. The combined alpha-/beta-blocker carvedilol is metabolically neutral and may provide the beneficial effects of beta blockade on cardiovascular events with a better side-effect profile [2]. In patients with diabetic CKD, adequate glycemic control remains an important step in preventing the progression of both autonomic and peripheral neuropathy [2].

26.2 Carpal Tunnel Syndrome

26.2.1 Definition and Clinical Importance

Carpal tunnel syndrome (CTS) is the result of compression of the median nerve at the wrist. CTS is the most common mononeuropathy in CKD affecting up to 30 % of dialysis patients [9]. The prevalence of CTS in CKD can be attributed to various factors. The presence of fistulae has been implicated in the development of CTS, as the prevalence of CTS in limbs with fistulae is ~30 % compared to ~12 % on the contralateral side [11]. The presence of amyloidosis or poor clearance of β2microglobulin may lead to localised deposition of amyloid in soft tissues leading to compression. Patients with CTS experience sensory symptoms in the hands including paraesthesia, numbness and pain with a characteristic feature of nocturnal exacerbation [9]. Symptoms are often more severe in the dominant hand and are not always confined to median nerve territory. Symptoms may involve any part of the hand and in some cases extend to more proximal regions of the arm. Long-standing disease can result in motor involvement causing weakness and wasting of muscles innervated by the median nerve, particularly abductor pollicis brevis.

26.2.2 Diagnosis

Diagnosis of CTS is made on clinical grounds, and exclusion of other pathologies, such as cervical spondylosis or generalised neuropathy, is important. Neurological examination may demonstrate a reduction in sensation in the median nerve territory or weakness of median-innervated muscles. Phalen's test may also aid in diagnosis. This test is conducted by placing the wrist into end-of-range palmar flexion for 1 min and aims to increase intratunnel pressure and thereby reproduce symptoms [9].

26.2.3 Management

Most patients with CTS should receive a trial of conservative treatment, with splinting of the wrist or a subcutaneous corticosteroid injection at the wrist. Injection of steroids should be avoided where CTS develops in the fistula arm. In patients who are refractory to conservative treatment or those in whom there is significant loss of muscle power or severe abnormalities of median nerve conduction, referral to a hand surgeon may be appropriate for endoscopic decompression of the nerve. While clinical improvement typically occurs with surgical decompression, outcomes are less favourable if the patient had fixed motor and sensory deficits prior to surgery [7]. In cases where amyloid deposition is suspected, biopsy specimens from the flexor retinaculum should be obtained during surgery.

26.3 Myopathy

26.3.1 Definition and Clinical Importance

Myopathy in CKD affects ~50 % of stage 5 CKD patients and is characterised by proximal muscle weakness and wasting, predominantly affecting the lower limbs. In addition, reduced exercise capacity, limited endurance and motor fatigue are prominent features resulting in substantial functional limitations and morbidity. The pathophysiology of uremic myopathy remains unclear though it typically appears with glomerular filtration rates less than 25 mL/min and progression tends to parallel decline of kidney function [12]. Possible aetiologies include hyperparathyroidism, metabolic bone disease with vitamin D deficiency, impaired potassium regulation, accumulation of uremic toxins and carnitine deficiency [1]. A clear association between malnutrition, specifically protein deficiency, and uremic myopathy has been demonstrated in elderly patients [12]. Furthermore, rates of uremic myopathy are higher in patients with diabetic CKD leading to a suggested role for insulin resistance in the development of this condition.

26.3.2 Diagnosis

Diagnosis of uremic myopathy is based on the demonstration of weakness in proximal hip girdle muscles [12]. There are no specific tests for uremic myopathy and electromyography, and creatine kinase levels are typically normal. Muscle biopsy reveals nonspecific features such as type II fibre atrophy and fibre splitting, although the procedure is not undertaken routinely due to its invasive nature and should be considered only after neurological referral.

26.3.3 Management

While no specific treatment exists for uremic myopathy, management requires treatment of potential contributing factors. Adequate management of hyperparathyroidism and vitamin D deficiency must be achieved. Nutritional supplementation, anaemia correction with erythropoietin and exercise programmes have been shown to improve exercise tolerance and neuromuscular function [12].

26.4 Cognitive Dysfunction and Dementia

26.4.1 Definition and Clinical Importance

Cognitive impairment is defined as a new deficit in two or more areas of cognitive function. Mild cognitive impairment is detectable by clinical assessment but does not impact daily functioning, while dementia is characterised by cognitive impairment and behavioural disturbance that interferes with independence and daily functioning [13]. CKD is an independent risk factor for progressive cognitive impairment and dementia. Cognitive impairment is present across the spectrum of CKD with both the prevalence and rate of progression inversely associated with level of kidney function [14]. As such, approximately 70 % of stage 5 CKD patients demonstrate moderate to severe cognitive impairment, with

greatest dysfunction reported in the domains of memory and executive function [1, 14].

The underlying cause of cognitive impairment has often been attributed to the various comorbidities and vascular complications that may be present in this patient cohort. There is a high prevalence of cardiovascular risk factors that lead to large and small vessel vascular disease in CKD such as hypertension, diabetes, age and smoking status [13]. A vascular aetiology for cognitive impairment is further supported by association between clinically silent cerebrovascular disease and degree of kidney impairment [1]. Additionally, patients in whom vascular nephropathy is the cause of CKD have a heightened risk of silent white matter disease. However, recent studies have shown that CKD is a risk factor of cognitive impairment independent of vascular and demographic variables [14]. Consideration should be given to secondary hyperparathyroidism and anaemia as potential risk factors for cognitive impairment in CKD. Excess parathyroid hormone levels in patients with CKD are postulated to interfere with neurotransmission in the CNS by increasing brain calcium content. Correction of anaemia has been demonstrated to improve measures of cognition. Dementia is a more powerful predictor of mortality than heart failure or stroke in stage 5 CKD patients and thus presents an important clinical complication [14]. Though moderate to severe cognitive dysfunction has been reported in ~40 % of dialysis patients, less than 3 % of the cohort had cognitive impairment documented as a comorbid condition in medical records, highlighting that the condition is under-recognised in routine clinical practice. There are no specific treatments for cognitive dysfunction in CKD aside renal transplantation [15].

26.4.2 Diagnosis

The mini-mental state examination (MMSE) is the most widely used method of assessment for cognitive impairment [13]. While a score of less than 24 on the MMSE indicates cognitive impairment, the instrument has low sensitivity for mild cognitive dysfunction [13]. Moreover, the MMSE is focused largely on the assessment of memory and attention at the expense of other cognitive domains such as executive function. Scores gained on the MMSE may also be influenced by a subject's educational and cultural background. In patients in whom MMSE is normal but where clinical suspicion for cognitive impairment is high, referral to a neuropsychology service is recommended for more intensive cognitive assessment. In all patients, cerebral imaging with computerised tomography scans (CT) or magnetic resonance imaging (MRI) is also recommended to exclude space-occupying lesions that may represent a treatable cause of cognitive impairment. Screening blood tests are also recommended to exclude other causes of cognitive impairment, including B12 deficiency and hypothyroidism.

26.4.3 Management

Recognition and documentation are crucial first steps in managing CKD patients with cognitive dysfunction or dementia. In patients with dementia, prompt initiation of conservative interventions, including patient and family education and non-pharmacological support plans, should be implemented. Pharmacological interventions are not widely recommended in CKD patients with dementia. Currently available pharmacological interventions for Alzheimer's disease (i.e. acetylcholinesterase inhibitors) have not been trialled in a CKD population [13].

26.5 Encephalopathy, Delirium and Seizures

26.5.1 Definition and Clinical Importance

Encephalopathy refers to diffuse alteration of brain function or structure, which manifests clinically as an altered level of consciousness. Aside

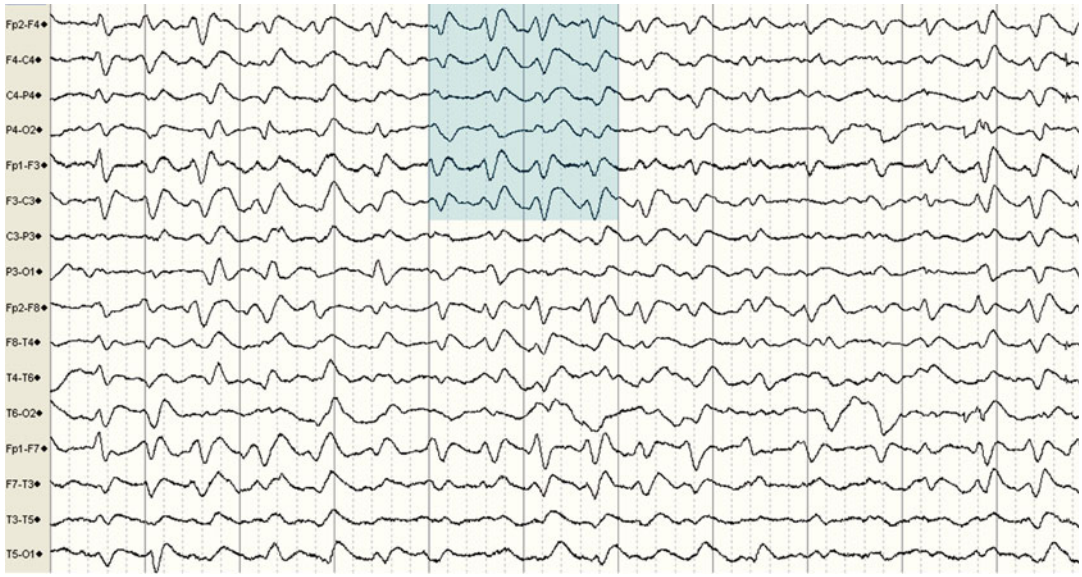

Fig. 26.4 Electroencephalograph for a chronic kidney disease patient who presented with drowsiness and confusion. Findings demonstrate a generalised slowing of the normal background with an excess of delta and theta waves, and abnormal triphasic waves (*blue highlighted section*), consistent with uremic encephalopathy

from renal impairment and the associated accumulation of toxins, other factors that have been implicated in the development of encephalopathy in CKD patients include thiamine deficiency, hypertension, fluid and electrolyte disturbances, drug toxicity, dialysis and transplant rejection [3, 16]. Features of uremic encephalopathy may have insidious onset and may present as a complex of non-specific symptoms related to altered mental functioning and/or motor disturbances, ranging from sensorial clouding to delirium and coma [3]. Early features can include fatigue, apathy, irritability and impaired concentration, while later features are more severe including confusion, disorientation, delirium, hallucinations, coma and seizures [5, 17]. Motor disturbances can accompany alterations in mental status and include tremor, fasciculations, asterixis and seizures, which may be generalised or focal [17]. Prompt recognition and diagnosis are important as encephalopathies may be reversible with treatment [17]. However, the rate of kidney failure seems to have an effect as symptoms are more pronounced and progress more rapidly in acute kidney disease [3, 5, 17].

26.5.2 Diagnosis

Laboratory blood tests should include a complete blood count, electrolyte panel, glucose, urea, creatinine, liver enzymes and ammonia [17]. Though no laboratory values or measures of kidney function correlate with symptoms of uremic encephalopathy, results may be beneficial to investigate cognitive disturbance due to changes in electrolyte or glucose levels. If the patient is febrile, a lumbar puncture may be necessary to investigate the possibility of meningitis or encephalitis [5, 17]. All patients should undergo cerebral imaging with CT or MRI to exclude a space-occupying lesion, haemorrhage or ischaemic stroke [1, 17]. Electroencephalography (EEG) should be undertaken in all patients and may demonstrate a generalised slowing of the normal background with excess delta and theta waves [5]. Triphasic sharp waves on EEG are considered a specific feature of metabolic encephalopathy (Fig. 26.4).

Management – The management of encephalopathy is focused on identification and treatment of the underlying cause. In all patients with CKD,

the first step in treatment of uremic encephalopathy is to correct any underlying metabolic disturbance. Symptoms are usually alleviated by dialysis treatment in patients with severe kidney failure, though mental status changes may take 1–2 days to improve [17]. However, rapid shifts in electrolyte concentrations, particularly sodium, may exacerbate symptoms and should be avoided. Anticonvulsants should not be prescribed prophylactically but in those patients who have developed seizures, treatment with anticonvulsants is required. Preferred medications in this setting include phenytoin, sodium valproate and carbamazepine [18].

Before You Finish: Practice Pearls for the Clinician

- Uremic neuropathy manifests in almost all patients with stage 5 CKD and is likely to be present at much earlier stages in patients with diabetic CKD. Painful symptoms may respond to treatment with gabapentin, while dietary potassium restriction, glycemic control and exercise strategies may be beneficial.
- Proximal weakness and exercise intolerance caused by uremic myopathy may respond to exercise programmes, adequate nutritional intake and treatment with erythropoietin.
- For CKD patients with carpal tunnel syndrome, wrist splints or corticosteriod injections may provide benefit.
- Patients with autonomic neuropathy may respond to sildenafil for impotence.
- Cognitive dysfunction and dementia are under-recognised and can be assessed using the mini-mental state examination or formal neuropsychological testing.
- Patients who have developed seizures require treatment with anticonvulsant medications. Preferred options include phenytoin, sodium valproate and carbamazepine.

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