Neurological complications of renal dialysis

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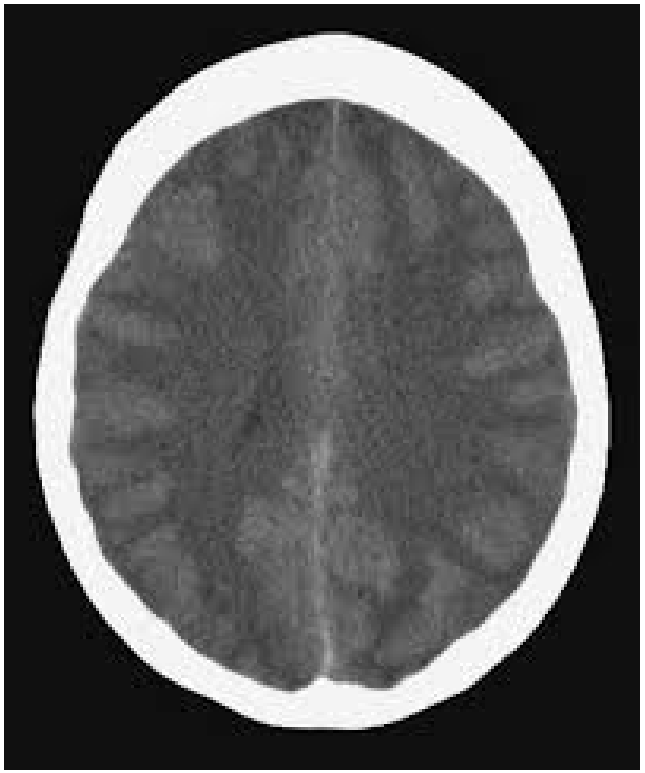
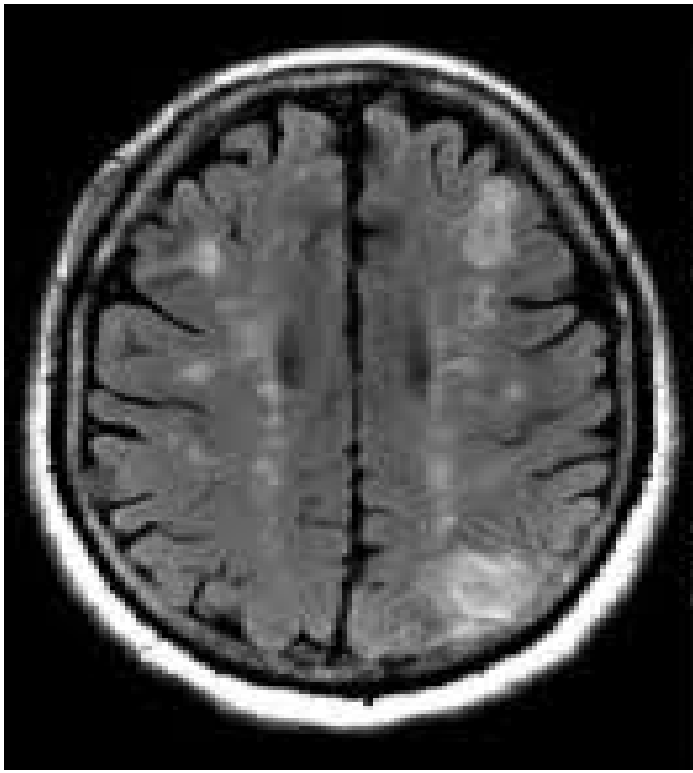
Case1.

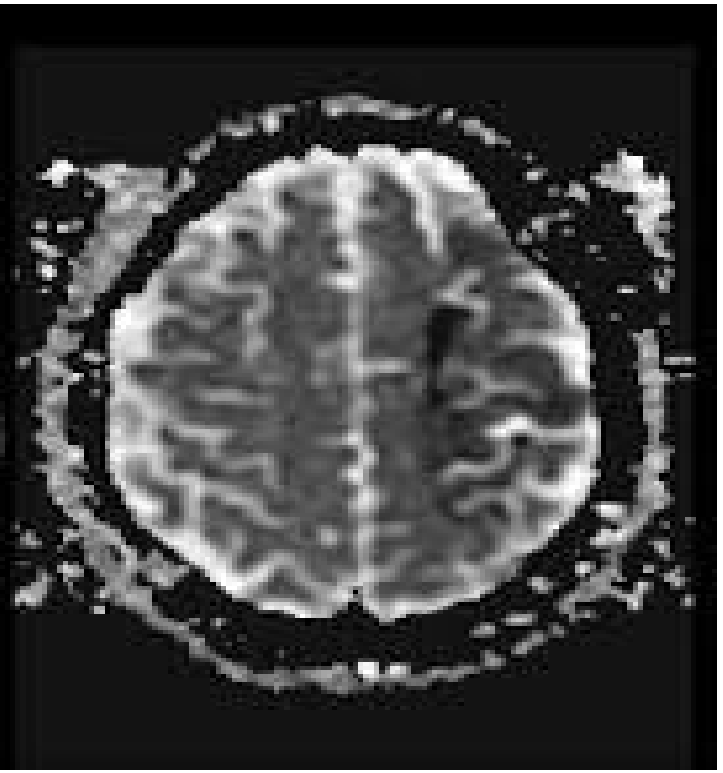
A 68-year-old lady with polycystic kidney disease, who had dialyzed for 10 years, was referred from a hemodialysis center with recurrent episodes of intradialytic hypotension.

She was noted to have weakness affecting her right arm, particularly her hand, with normal tone and reflexes. The weakness was global rather than flexor or extensor, and not in a nerve or root distribution.

MRI:







- Diagnosis?

Neurological complications of renal dialysis and transplantation

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ABSTRACT

Neurological complications from renal replacement therapy contribute significantly to morbidity and mortality in patients with renal failure. Such complications can affect either the central or peripheral nervous systems. Most neurological disturbances associated with the uraemic state do not respond fully to renal replacement therapy. There are also complications specifically associated with dialysis and transplantation. A multidisciplinary approach, involving both nephrologists and neurologists, is critical for the diagnosis and effective management of these disorders.

INTRODUCTION

The most recent UK renal registry report noted that 60 000 patients were receiving renal replacement therapy at the end of 2014, of whom 7411 had started renal replacement therapy during that year.[1] Transplantation was the most common treatment (53%); haemodialysis was used in 41% and peritoneal dialysis in 6% of renal replacement therapy patients.[1] The kidney and transplant service at Imperial College Healthcare NHS Trust, London,

Despite therapeutic advances in dialysis and transplantation, the well-described neurological complications of uraemia such as encephalopathy, neuropathy and myopathy remain serious concerns and can lead to functional impairment.[3] Although the spectrum of neurological disease in renal failure has changed with the advent of dialysis, many patients still experience chronic uraemic complications. The underlying reasons for this are not clear, but probably relate to the inability of standard dialysis to clear 'middle molecules'—a range of toxins comprising mostly low-molecular-weight peptides and proteins: 300–12 000 kDa.[4] Dialysis itself can cause additional neurological problems in these patients (table 1). With progression from dialysis to renal transplantation, immunosuppressive therapy may cause various neurological disturbances.[5] Our experience suggests that neurological presentations in renal replacement therapy patients are often multifactorial, and require several problems to be addressed.

Review article

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Neurological complications in chronic kidney disease

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Abstract

Patients with chronic kidney disease (CKD) are frequently afflicted with neurological complications. These complications can potentially affect both the central and peripheral nervous systems. Common neurological complications in CKD include stroke, cognitive dysfunction, encephalopathy, peripheral and autonomic neuropathies. These conditions have significant impact not only on patient morbidity but also on mortality risk through a variety of mechanisms. Understanding the pathophysiological mechanisms of these conditions can provide insights into effective management strategies for neurological complications. This review describes clinical management of neurological complications in CKD with reference to the contributing physiological and pathological derangements. Stroke, cognitive dysfunction and dementia share several pathological mechanisms that may contribute to vascular impairment and neurodegeneration. Cognitive dysfunction and dementia may be differentiated from encephalopathy which has similar contributing factors but presents in an acute and rapidly progressive manner and may be accompanied by tremor and asterixis. Recent evidence suggests that dietary potassium restriction may be a useful preventative measure for peripheral neuropathy. Management of painful neuropathic symptoms can be achieved by pharmacological means with careful dosing and side effect considerations for reduced renal function. Patients with autonomic neuropathy may respond to sildenafil for impotence. Neurological complications often become clinically apparent at end-stage disease, however early detection and management of these conditions in mild CKD may reduce their impact at later stages.

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leurological complications in chronic kidney disease patients

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Chronic kidney disease and neurological disorders: are uraemic toxins the missing piece of the puzzle?

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Stroke

SPECIAL REPORT

Chronic Kidney Disease and Cerebrovascular Disease

Consensus and Guidance From a KDIGO Controversies Conference

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ABSTRACT: The global health burden of chronic kidney disease is rapidly rising, and chronic kidney disease is an important risk factor for cerebrovascular disease. Proposed underlying mechanisms for this relationship include shared traditional risk factors such as hypertension and diabetes, uremia-related nontraditional risk factors, such as oxidative stress and abnormal calcium-phosphorus metabolism, and dialysis-specific factors such as cerebral hypoperfusion and changes in cardiac structure. Chronic kidney disease frequently complicates routine stroke risk prediction, diagnosis, management, and prevention. It is also associated with worse stroke severity, outcomes and a high burden of silent cerebrovascular disease, and vascular cognitive impairment. Here, we present a summary of the epidemiology, pathophysiology, diagnosis, and treatment of cerebrovascular disease in chronic kidney disease from the Kidney Disease: Improving Global Outcomes Controversies Conference on central and peripheral arterial disease with a focus on knowledge gaps, areas of controversy, and priorities for research.

Key Words: atrial fibrillation ■ diagnosis ■ dialysis ■ epidemiology ■ uremia

Aminoff's Neurology and General Medicine

FIFTH EDITION

MICHAEL J. AMINOFF
S. ANDREW JOSEPHSON

Neurological complications from renal replacement therapy contribute significantly to morbidity and mortality in patients with renal failure.

Such complications can affect either the central or peripheral nervous systems.

Most neurological disturbances associated with the uraemic state do not respond fully to renal replacement therapy.

There are also complications specifically associated with dialysis and transplantation.

A multidisciplinary approach, involving both nephrologists and neurologists, is critical for the diagnosis and effective management of these disorders.

Neurological complication related to:

Sometimes relate to systemic conditions—particularly diabetes mellitus and autoimmune diseases leading directly to both neurological and kidney disease.

Secondary to dialysis or subsequent to renal transplantation.

Most neurological dialysis complications develop in both haemodialysis and peritoneal dialysis.

Complications associated with haemodynamic instability are more likely in those undergoing haemodialysis.

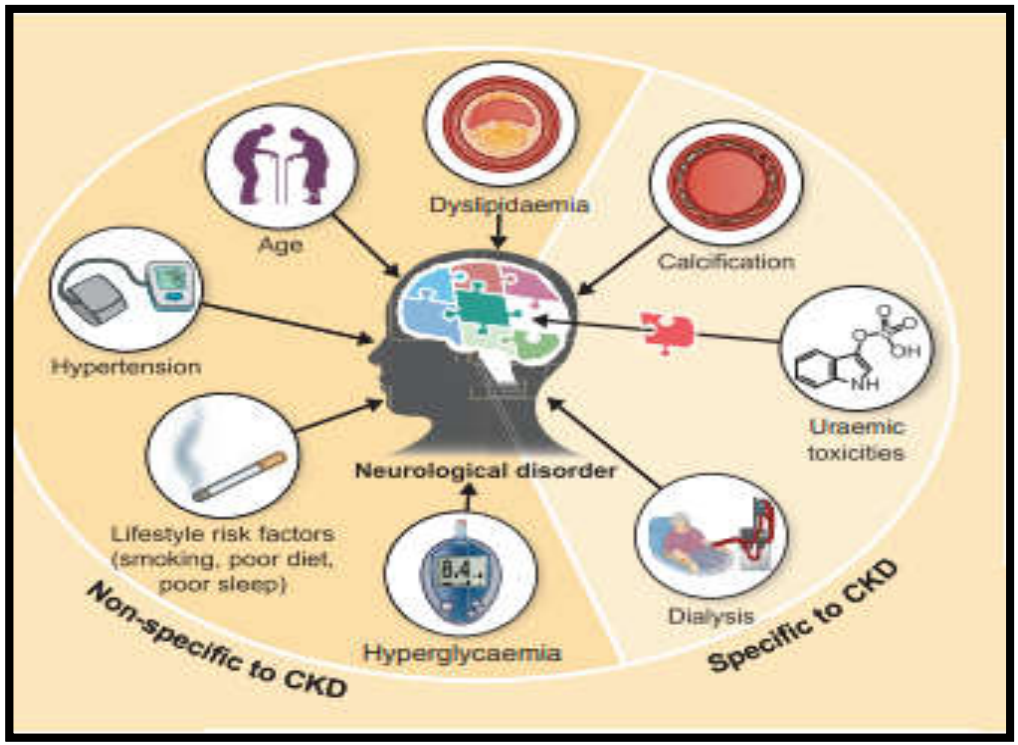
Dialysis headache is probably less common in peritoneal dialysis, although the underlying mechanisms explaining this difference are unclear*

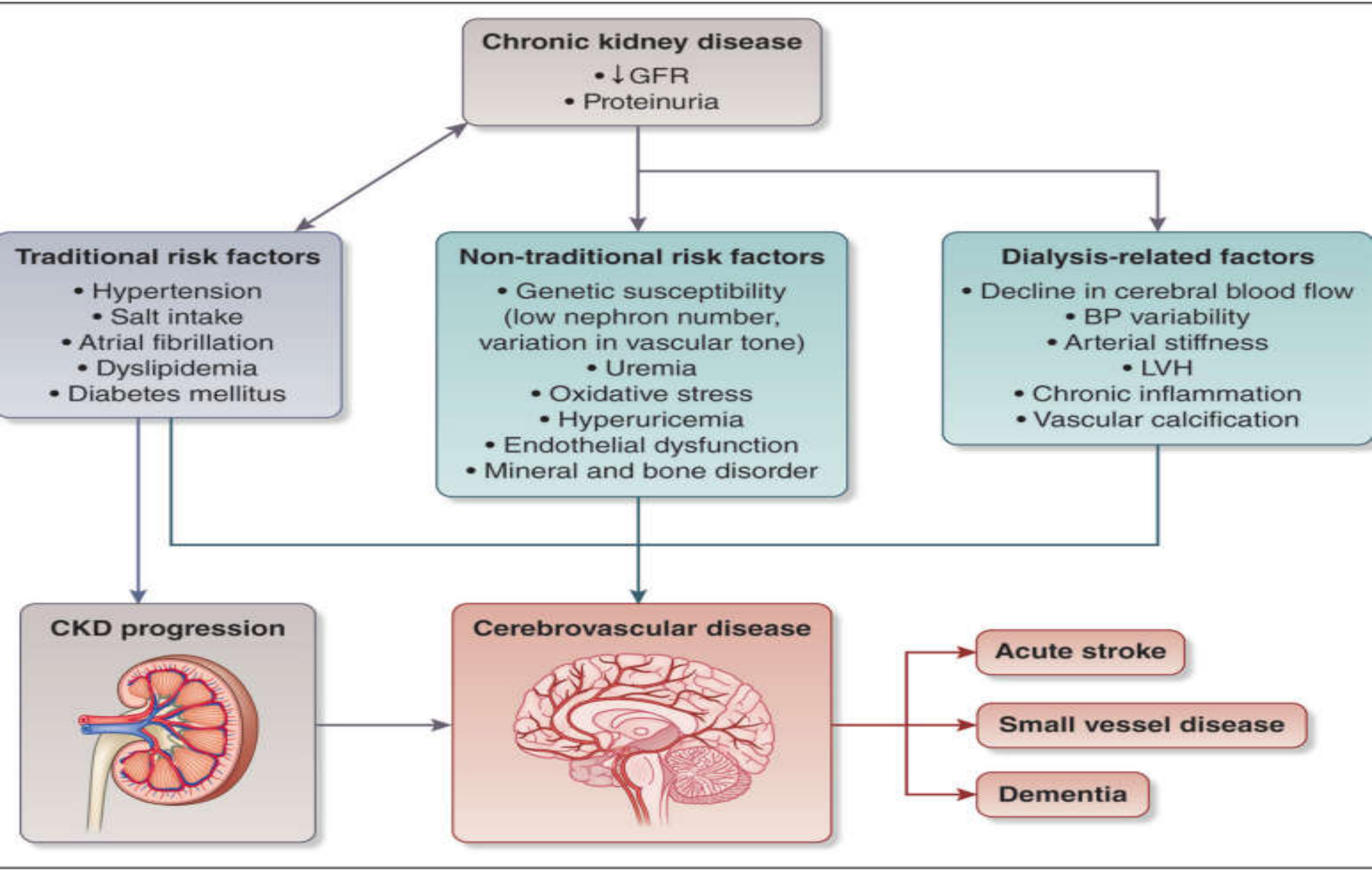
*Stojimirovic B, Milinkovic M, Zidverc-Trajkovic J, et al. Dialysis headache in patients undergoing peritoneal dialysis and hemodialysis. Ren Fail 2015;37:241–4.

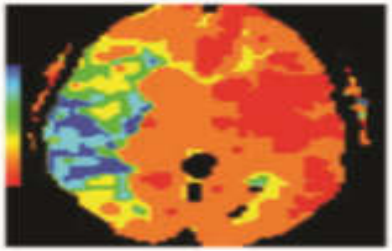
Table 1 Neurological complications secondary to dialysis

Central nervous system	Cerebral haemorrhage Cerebral thrombosis Central pontine myelinolysis Wernicke's encephalopathy Dialysis dementia Cognitive impairment Disequilibrium syndrome Anterior ischaemic optic neuropathy Posterior reversible encephalopathy syndrome
Peripheral nervous system	Vascular access related nerve injury Carpal tunnel syndrome Peripheral neuropathy
Others	Haemodialysis headache Dialysis-induced hypotension Drug toxicity

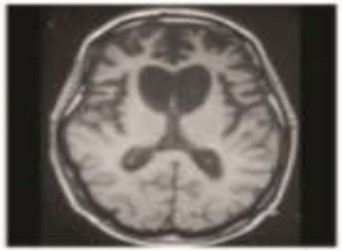
Central nervous system



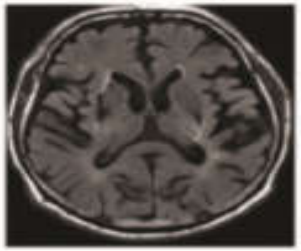

Chronic kidney disease
• ↓GFR
• Proteinuria
Traditional risk factors
• Hypertension
• Salt intake
• Atrial fibrillation
• Dyslipidemia
• Diabetes mellitus
Non-traditional risk factors
• Genetic susceptibility (low nephron number, variation in vascular tone)
• Uremia
• Oxidative stress
• Hyperuricemia
• Endothelial dysfunction
• Mineral and bone disorder
Dialysis-related factors
• Decline in cerebral blood flow
• BP variability
• Arterial stiffness
• LVH
• Chronic inflammation
• Vascular calcification
CKD progression
Cerebrovascular disease
Acute stroke
Small vessel disease
Dementia



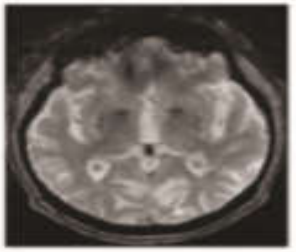
Stroke



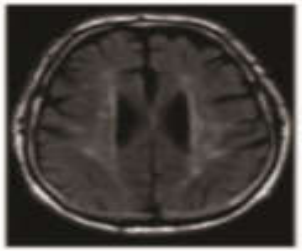
Cognitive disorders



Silent brain infarcts



Microbleeds



White matter disease

Cerebrovascular and neurological diseases

raditional CV risk factors

hypertension

diabetes

cholesterol

smoking

demographics

Non-traditional CV risk factors

oxydative stress

endothelial dysfunction

Uremic Toxins

inflammation

calcification

Others

anaemia

dialysis-related factors

CKD treatments

CKD

Cerebral hemorrhage

Chronic uremia, intra dialytic anticoagulation, inadequate control of hypertension and concurrent use of blood thinners such as aspirin increase the risk of hemorrhagic events.

Uremia results in platelet dysfunction as well as abnormal interactions between platelets and the vessel wall, increasing any bleeding tendency

SDH has a 20 times higher incidence than the general population

The location of hemorrhage is also more likely to be lobar, rather in the deep basal ganglia, brainstem or cerebellar bleeds.

The risk of systemic bleeding risk can be reduced by regional anticoagulation and minimising heparin use

Patients who have had a recent intracerebral hemorrhage, those who are actively bleeding from another site or those at a high risk of bleeding can undergo dialysis without anticoagulation (heparin-free dialysis).

In retrospective more than 2500 patients on maintenance haemodialysis found a prevalence of non-traumatic subdural haemorrhage of 0.4%, with an overall annual incidence of 189 per 100 000 patients.

There was no association with comorbidities such as hypertension and diabetes, or with the use of anti-platelet and anticoagulant medication*

*Power A, Hamady M, Singh S, et al. High but stable incidence of subdural haematoma in haemodialysis-a single-centre study. Nephrol Dial Transplant 2010;25:2272–5.

Treatment of uremic bleeding

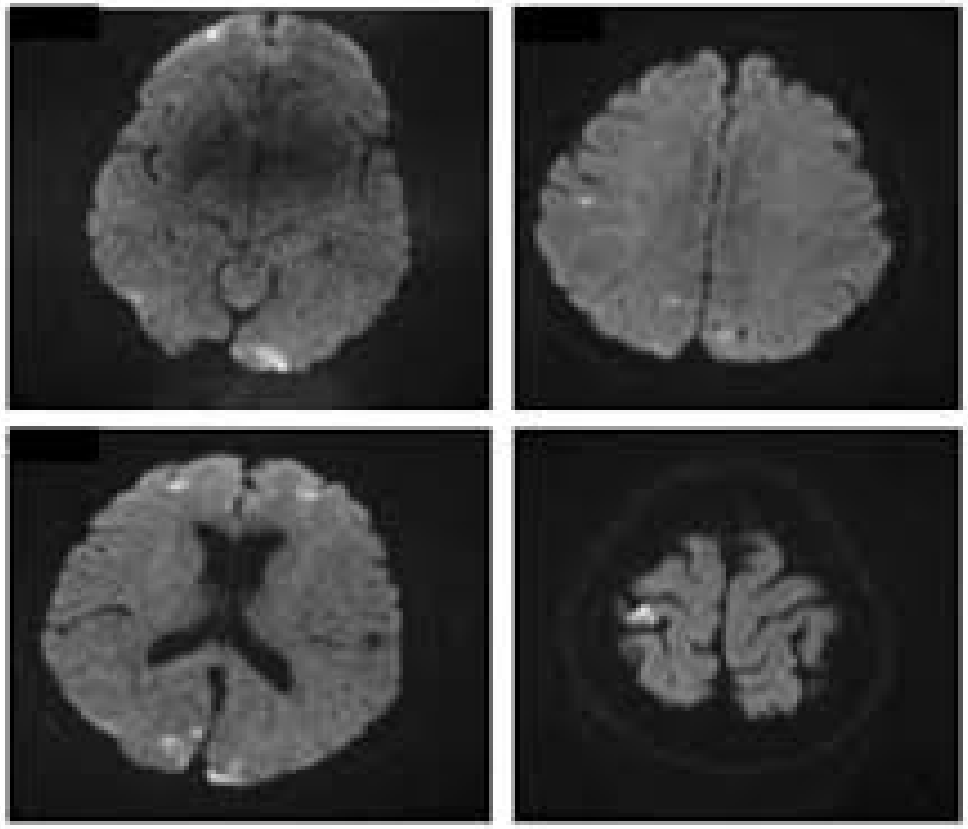
Treatment	Proposed Mechanism	Dose	Time of onset
DDAVP	Increase release of factor VIII-von Willebrand factor multimers	0.3–0.4 mcg/kg IV	1–4 h
Recombinant erythropoietin	Increases reticulated platelets Increases circulating RBC displacing platelets toward endothelium Enhances platelet aggregation Improved platelet signaling NO scavenger	40–150U/kg IV three times per week	Between 7 days and up to 9 weeks (to achieve Hct>30%)
Cryoprecipitate	Increases proportion of clotting factors in plasma	10 bags IV American Red Cross prepared	Within 4–12 h
Estrogen	Decrease production of L-arginine, precursor to NO leading to ↑TxA_2 & ADP formation Possibly decreases antithrombin III and protein S levels & increases factor VII concentrations	0.6 mg/kg IV daily for 5 consecutive days Oral & transdermal may also be effective	6 h; maximum effect 5–7 days

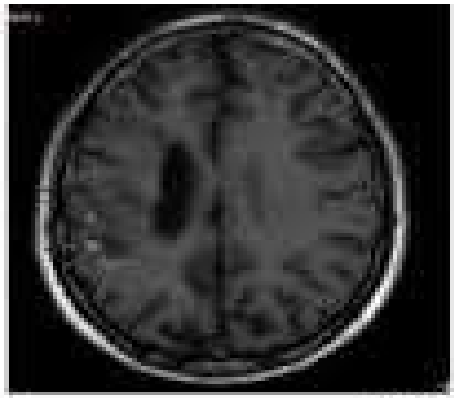
DDAVP = 1-deamino-8-D-arginine vasopressin | Hct = Hematocrit | NO = nitric oxide | TxA_2=Thromboxane A_2 |ADP=adenosine diphosphate

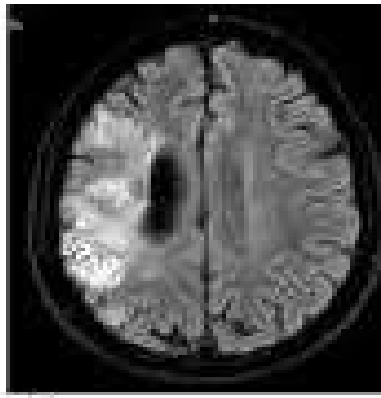
Cerebral thrombosis

- In long-term dialysis patients stroke has a prevalence of 17% compared to 10% for nondialysis CKD patients and 4% for the general population*
- In addition, post-stroke outcomes in dialysis patients are poor with mortality rates 3–5 times higher than non-CKD patients**
- Hemodialysis patients appear to be at higher stroke risk compared with peritoneal and kidney transplant patients.
- Recent meta-analysis data have confirmed that there is a strong inverse relationship between renal function and stroke with a 7% increase in risk per 10mL/min decline in eGFR ***

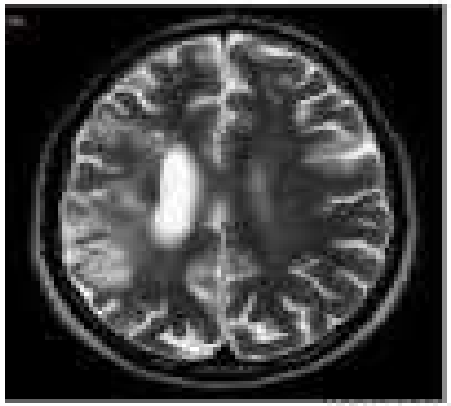
Bugnicourt JM, Godefroy O, Chillon JM, et al. Cognitive disorders and dementia in CKD: the neglected kidneybrain axis. J Am Soc Nephrol 013; 24: 353–363.
*Arnold J, Sims D and Ferro CJ. Modulation of stroke risk in chronic kidney disease. Clin Kidney J 2016; 9: 29–38
*Masson P, Webster AC, Hong M, et al. Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis. Nephrol Dial ansplant 2015; 30: 1162–1169

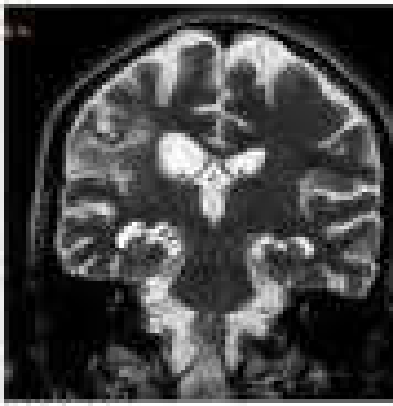






DWI and FLAIR



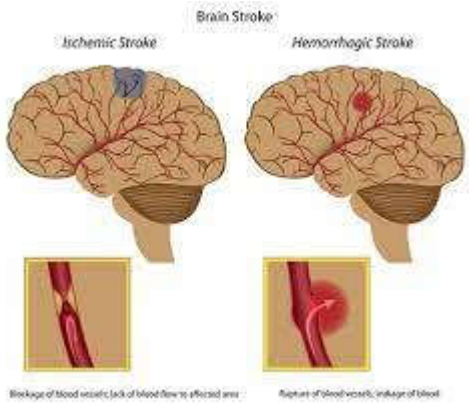


T2WI Axial and Coronal

Risk factors

hypertension,
hypercholesterolaemia,
atrial fibrillation,
bleeding diatheses and
blood vessel wall fragility
anaemia,
bone mineral disorder
dialysis itself

The clot formed in CKD is structurally and functionally different to clot formed where renal function is normal; this may explain why patients with CKD are at higher risk of thrombosis, but are paradoxically, too, at higher risk of bleeding



DIAGNOSTIC CONSIDERATIONS

Recent meta-analysis of 14 studies (5727 CT angiography/CT perfusion imaging and 981 noncontrast CT patients) found that the risk of acute kidney injury was significantly lower for patients who had received contrast compared with those who did not (odds ratio [OR], 0.47 [95% CI, 0.33–0.68]; P<0.001).

Although more recent evidence suggests that the risk associated with the newer, more stable group II gadolinium-based contrast agent (gadobenate dimeglumine, gadobutrol, gadoterate meglumine, or gadoteridol) is quite low (<0.07%)

However, in general, patients with kidney disease should not be denied CT angiography/ CT perfusion imaging or gadolinium-free MR imaging as they appear to be safe.

Diagnosis and management

Acute treatment is similar between non-dialysis CKD patients and the general population.

However, for CKD patients on dialysis, there is a higher risk of intracerebral haemorrhage compared to the general population when administering tissue plasminogen activator, possibly due to endothelial and platelet dysfunction in these patients*

Although there is clearly a lack of evidence in this area, we would concur with the guidelines that recommend intravenous thrombolysis use in otherwise-eligible patients with CKD.

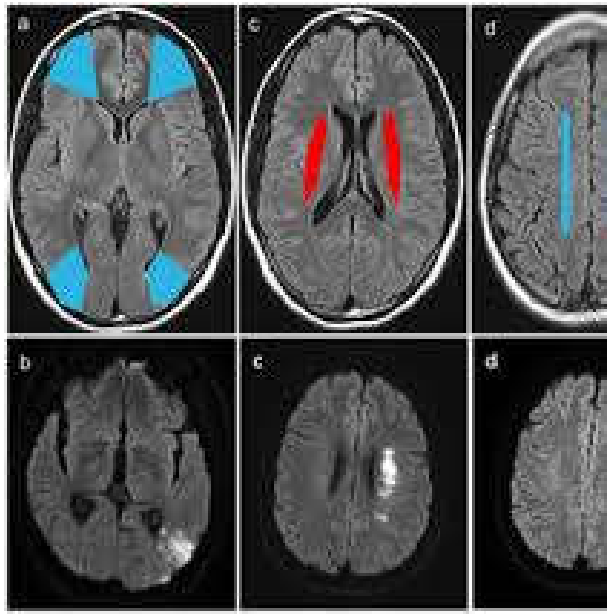
The efficacy of mechanical thrombectomy as an alternative to thrombolysis in CKD patients is yet to be adequately established.

*Dad T and Weiner DE. Stroke and chronic kidney disease: epidemiology, pathogenesis, and management across kidney disease stages. Semin Nephrol 2015; 35: 311–322.

Hyperhomocysteinaemia is highly prevalent in CKD and has been associated with stroke.

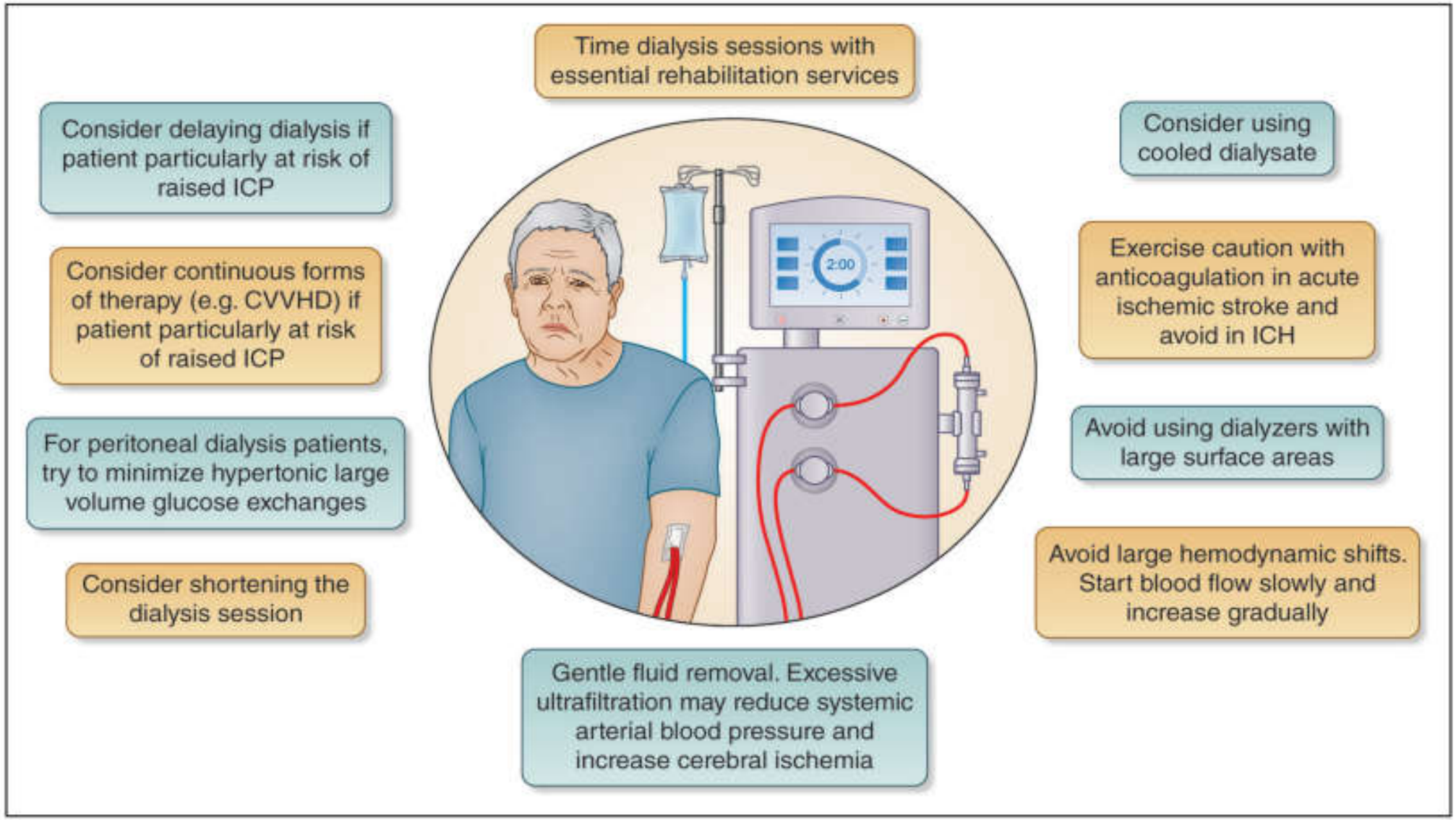
However, clinical trials have failed to provide compelling evidence that vitamin therapy with folic acid provides benefit in reducing stroke risk

The process of dialysis causes significant haemodynamic shifts, these changes in blood flow are hypothesized to adversely affect end organs and result in perfusion related brain injury



Erythropoietin-stimulating agents increase the risk of stroke but could improve cognitive function in dialysis CKD.

Suggestions for dialysis prescribing in acute stroke



le 3. Recommendations for the Primary and Secondary Prevention of Stroke in CKD

	Primary Prevention	Secondary Prevention	Source (and strength) of reco mendation
ervention:			
estyle modifications	Smoking cessation, healthy diet, weight restriction, and regular exercise should all actively encouraged.	As per primary prevention.	Expert consensus
tiplatelet therapy	There is currently insufficient evidence to support the use of antiplatelet therapy for primary prevention.	Antiplatelet therapy for secondary prevention is uniformly recommended	NICE[87] and KDIGO[88] guidelin
ticoagulation	In general, anticoagulation is recommended for the primary prevention of stroke with AF in this group. This is a high-risk group in which risk prediction tools such as CHA_2DS_2-VASc may have limited utility. For those with eGFR >30 mL/min per 1.73 m^2, first-line treatment should be with a NOAC. For those with eGFR 15–29 mL/min per 1.73 m^2, the choice of agent should depend on the trajectory of their renal function and should, therefore, be discussed with their nephrologist. For those with an eGFR <15 mL/min per 1.73 m^2, the decision to anticoagulate and the choice of agent should be discussed with their nephrologist.	As per primary prevention but we would advise having an even lower threshold to anticoagulate. The AHA/ACC[89] recommend using either a apixaban or warfarin in dialysis-dependent patients though long-term safety data on the former is lacking, and there is a risk of vascular calcification with the latter. Consider left atrial appendage occlusion devices in those with additional bleeding concerns as they have been shown to be safe and effective in advanced CKD after the initial periprocedural period.	AHA/ACC[89] guid lines (LOE IIb)
al blockade tiplatelet+low-dose AC)	There may be a role for dual pathway blockade in patients with CKD (eGFR 30-59 mL/min per 1.73 m^2) who have chronic coronary artery or peripheral artery disease and who are thought to be at low risk of bleeding.	There is no evidence to support the use of dual pathway blockade for secondary prevention at this time.	Expert consensus
od pressure control	Tight blood pressure control to <120/80 mm Hg is essential. RAS blockers are the antihypertensive agents of choice.	As per primary prevention.	KDIGO updated 2021 blood press guidelines (LOE IIb)[89a]
id-lowering therapy	As per KDIGO,[90] if >50 y and CKD present, treat with statin or statin/ezetimibe. In dialysis-dependent CKD, do not start statins de novo but continue if already taking.	We would recommend statin therapy for all patients with CKD who have had a stroke event. As per KDIGO guidelines,[90] statins may be continued in dialysis patients who are already taking them but should not be started unless very high LDL-C levels (3.8 mmol/L).	KDIGO[90] guidelin (LOE Ia for those >50 y and IIa-c fo dialysis recomme dations)
LT-2 inhibitors	We recommend treating all diabetic CKD patients with an eGFR > 30 mL/min per 1.73 m^2 with an SGLT-2 inhibitor.	We recommend treating all diabetic CKD patients with an eGFR >30 mL/min per 1.73 m^2 with an SGLT-2 inhibitor.	KDIGO[91] guidelin (LOE Ia)
rotid interventions	We would not recommend carotid revascularization for patients with CKD with asymptomatic disease.	Consider carotid revascularization in nondialysis patients with CKD with symptomatic moderate-severe stenosis, and in very high-risk dialysis patients with symptomatic disease.	Society for Vascu Surgery guideline
lysis-related erventions	Careful attention to blood pressure and volume control when a patient is first about to start dialysis. Maintain hemoglobin values between 100 and 120 g/L.	As per primary prevention.	KDIGO[93] guidelin (LOE IIc)

Central pontine myelinolysis

Rapid plasma osmotic fluctuations during hemodialysis can result in centra pontine myelinolysis (osmotic demyelination syndrome).

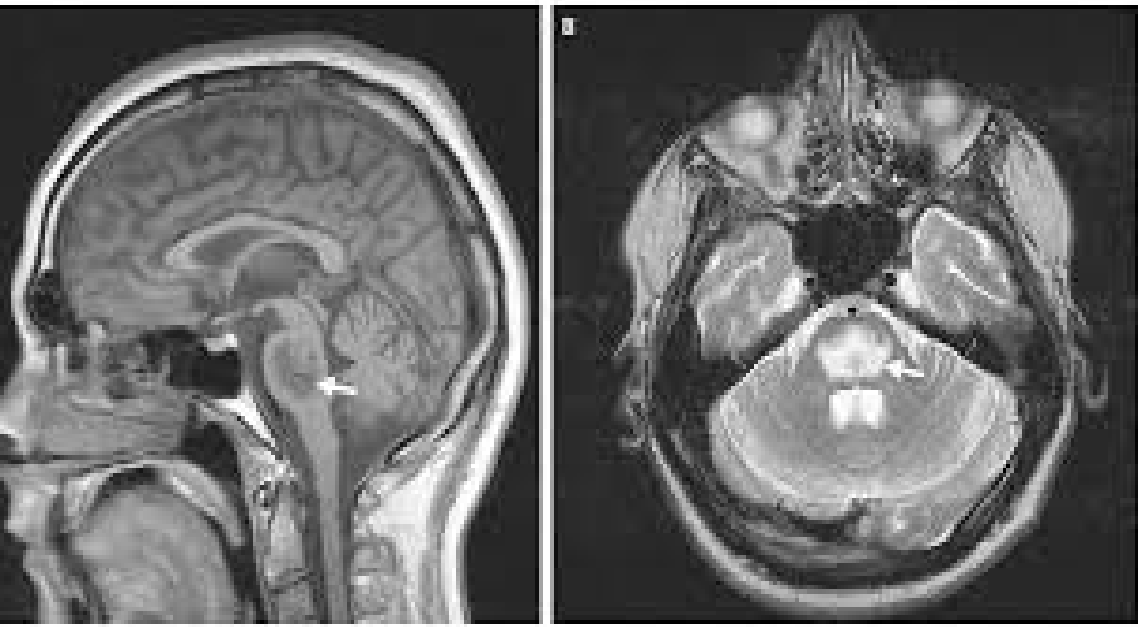
This is more likely in patients with chronic hyponatraemia and elevated serum osmolality.

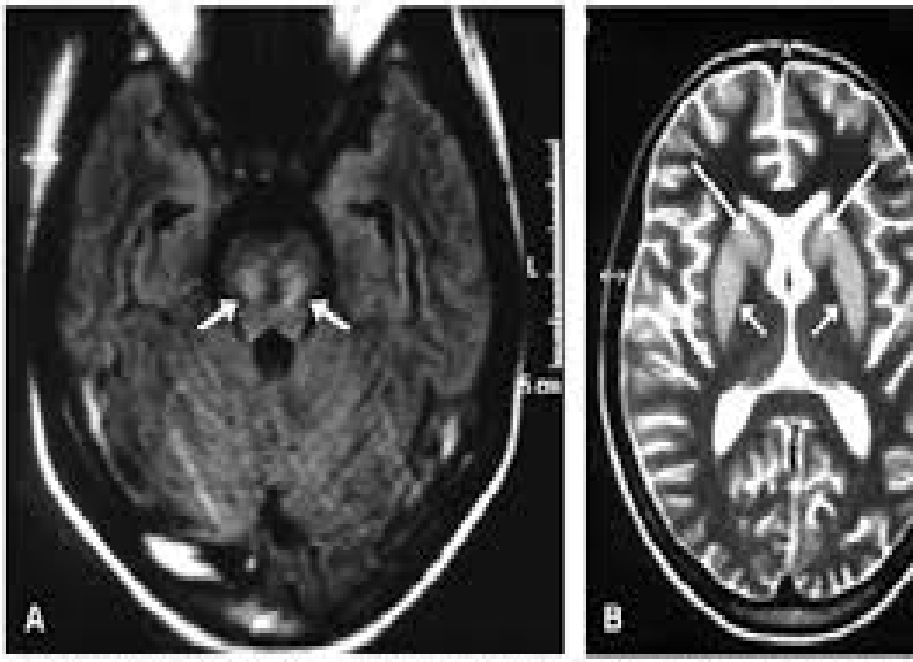
The initial symptoms, such as dysarthria, dysphagia and limb weakness, ca mimic a stroke.

MRI shows characteristic oedema in the pons and extrapontine regions.

Clinicians must correct serum sodium concentrations only slowly (6–8mmol/ day) by reducing the dialysate sodium concentration and by slowing rate of blood flow during dialysis.*

zo MA, Frediani F, Granata A, et al. Neurological complications of hemodialysis: state of the art. J Nephrol 2012;25:170–82.

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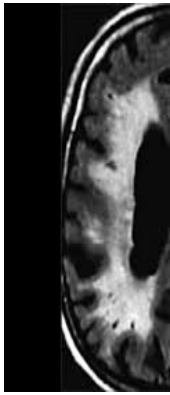
B

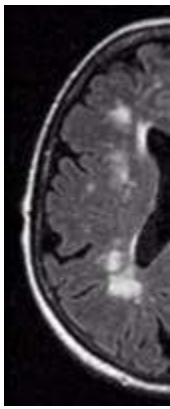
Dialysis dementia

The reported prevalence of cognitive impairment in dialysis is estimated at between 30% and 60% while less than 5% of patients have clinically documented histories of cognitive impairment*

Dialysis-associated dementia has been described ‘with aluminium neurotoxicity widely recognized as the causative factor

High rates of cardiovascular risk factors contribute to development of cerebrovascular disease. Cognitive impairment secondary to vascular disease is probably more common than Alzheimer’s disease in haemodialysis patients





McQuillan R and Jassal SV. Neuropsychiatric complications of chronic kidney disease. Nat Rev Nephrol 2010; 6
71–479.

Many studies have also noted that hemodialysis patients have cognitive impairment more often than peritoneal dialysis patients*

Rapid fluctuations in blood pressure, electrolytes and osmolality with haemodialysis may cause cerebral ischaemic injury leading to cognitive impairment.

Peritoneal dialysis does not lead to such rapid changes, the high glucose-based dialysate leading to secondary metabolic disorders probably contributes to cognitive impairment.

Volfgram DF, Szabo A, Murray AM, et al. Risk of dementia in peritoneal dialysis patients compared with modialysis patients. Perit Dial Int 2015;35:189–98.

Diagnosis and management

- Mini-Mental State Examination (MMSE)
- Modified MiniMental State Examination,
- Kidney Disease Quality of Life Cognitive Function subscale,
- Montreal Cognitive Assessment,
- MRI is also essential and may identify silent brain infarcts, microbleeds and white matter disease
- ❖B12 deficiency and hypothyroidism, should be investigated through blood test screening.

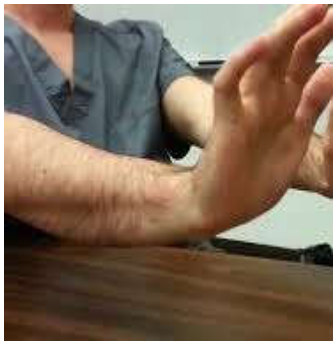
Pharmacological interventions are of limited utility in cognitive lysfunction due to CKD and are not widely recommended

Encephalopathy and delirium

An acute diffuse alteration of brain function or structure induced by a toxic or metabolic disturbance

Uraemic encephalopathy

- Insidious onset and early features can be non-specific such as fatigue, apathy, irritability and impaired concentration
- Alterations in mental status can be accompanied by generalised or focal motor disturbances including tremor, fasciculations, asterixis and seizures.
- Later features are more severe including confusion, disorientation, delirium, hallucinations, coma and seizures



Causes

- Uraemic toxins :Guanidino compounds , excess PTH may disrupt cerebral function via increased brain calcium content
- Wernicke’s encephalopathy
- Hypertensive encephalopathy such as posterior reversible encephalopathy syndrome (PRES)
- Rejection encephalopathy
- Sepsis
- Dialysis disequilibrium syndrome
- Drug toxicity

Disequilibrium syndrome

Cerebral oedema and raised intracranial pressure probably contribute to dialysis-related disequilibrium syndrome(water in to brain)

This was first described over 50 years ago but is now very rare.

It can develop in any patient undergoing haemodialysis but most commonly occurs after the first session.

The initial symptoms range between headache, muscle twitching, restlessness and nausea, and progression of cerebral oedema can result in coma and death.

The simplest way to prevent disequilibrium syndrome is to use haemofiltration instead of haemodialysis.

If using haemodialysis, recommended ways to reduce the risk of occurrence include slowly reducing serum urea concentrations, taking a gentle approach with new dialysis patients, and using high sodium-containing dialysates or other osmotic agents.*

*Zepeda-Orozco D, Quigley R. Dialysis disequilibrium syndrome. Pediatr Nephrol 2012;27:2205–11.

Parkinson's disease

A few large epidemiologic studies have found an increased risk of Parkinson's disease risk in patients with CKD. All the studies were performed in Asia (in Taiwan and South Korea).

In a Taiwanese study of patients with newly diagnosed ESRD versus controls, the incidence of Parkinson's disease was 1.55-fold higher in the ESRD cohort than in the control cohort.

CKD and Parkinson's disease share some pathophysiologic mechanisms, such as oxidative stress, hypertension, vitamin D deficiency and anaemia

Case2.

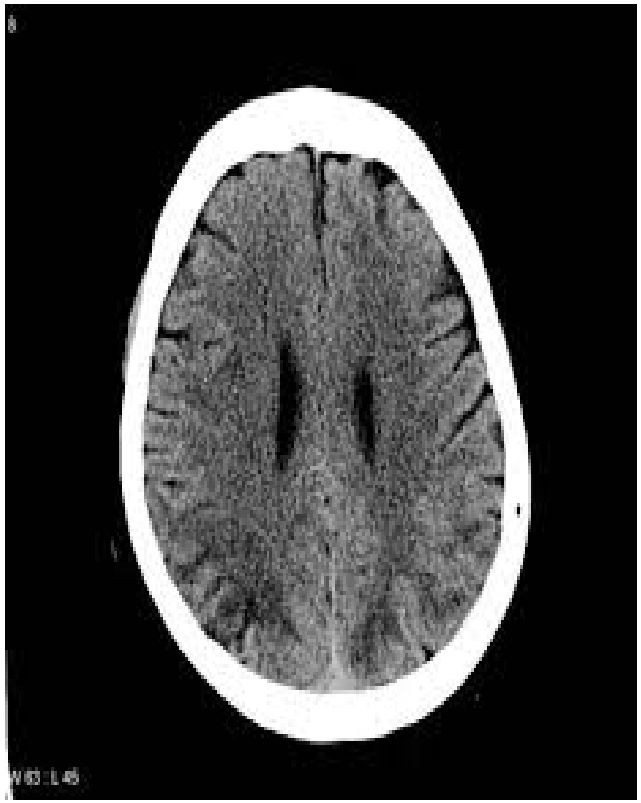
A 12-year-old boy, was diagnosed as having steroid-dependent nephrotic syndrome at the age of 4 years.

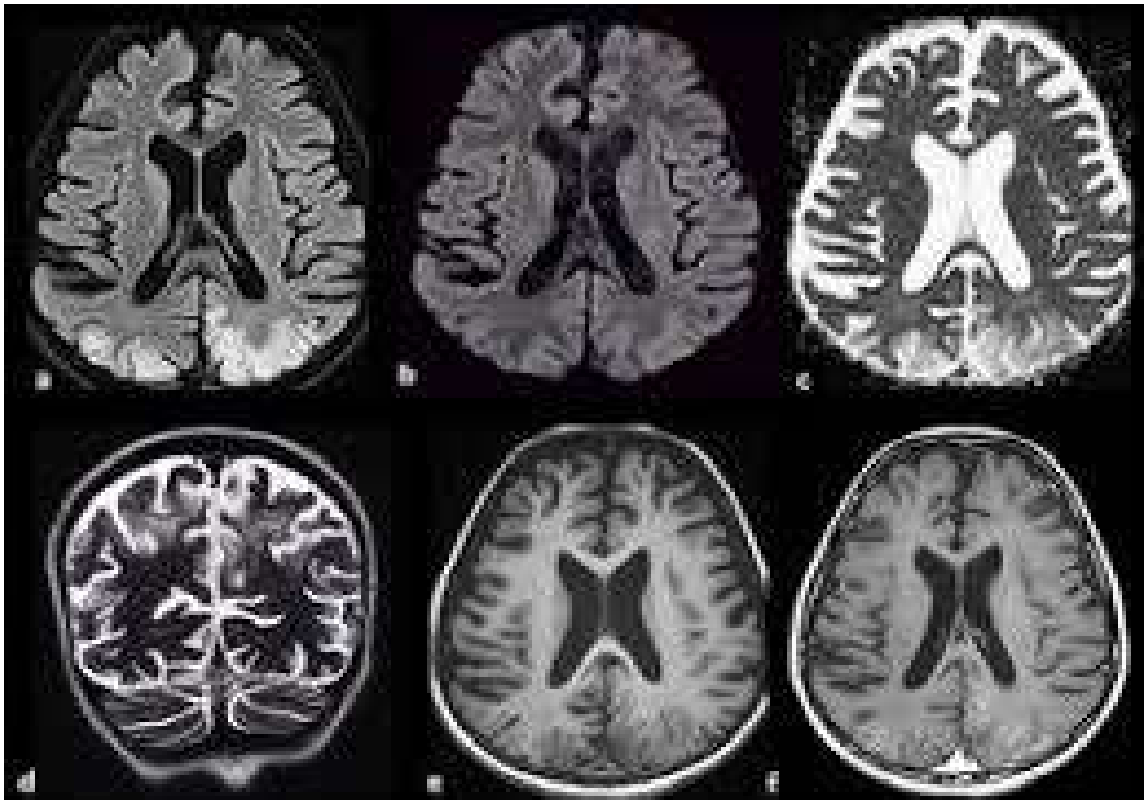
He developed severe renal failure and was initiated on hemodialysis.

He had seizures and headache secondary to hypertension.

serum creatinine is 5.2 mg/dl.

MRI:





- Diagnosis?

Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological disorder predominantly affecting cerebral white matter and is often associated with a rapid increase in blood pressure.

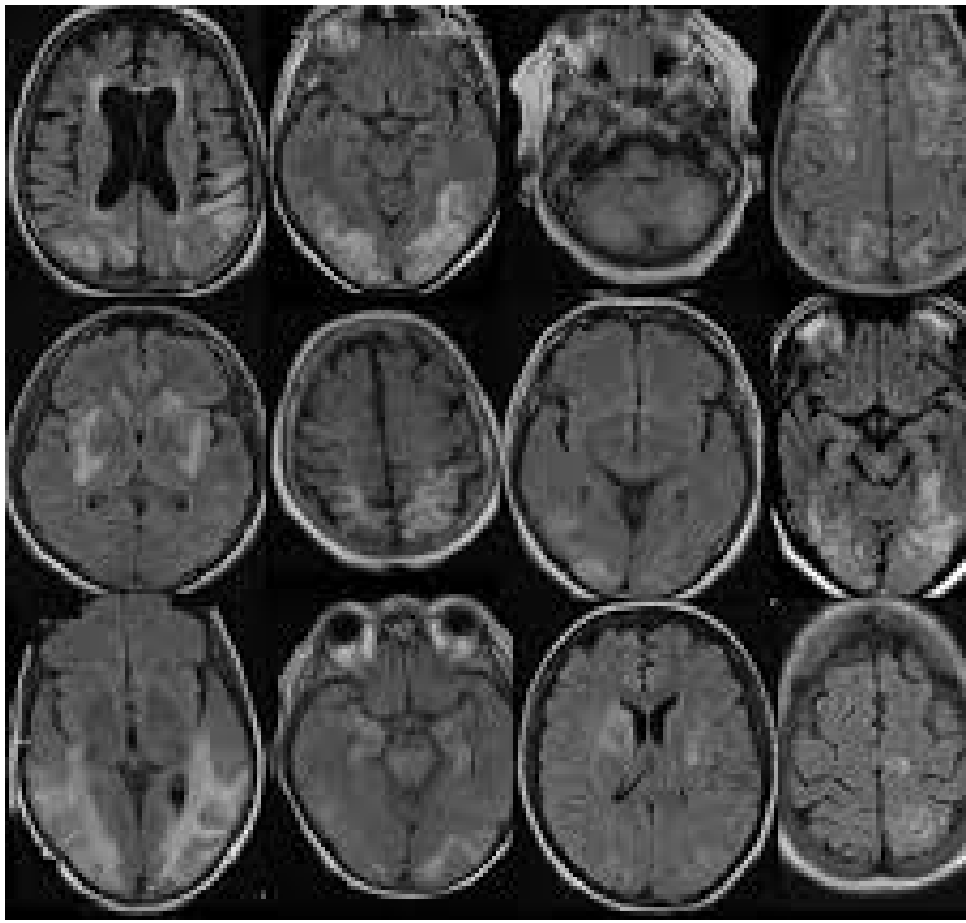
It is also, rarely, associated with systemic autoimmune diseases such as systemic lupus erythematosus.

Calcineurin inhibitors such as cyclosporine and tacromilus, which are used for immunosuppression in transplant recipients, are also known to cause PRES.

PRES typically presents with headache, visual disturbance, altered mental state and seizures.

MRI is essential for the diagnosis; typically, but not exclusively, this shows vasogenic oedema in the deep white matter of the occipital and parietal lobes

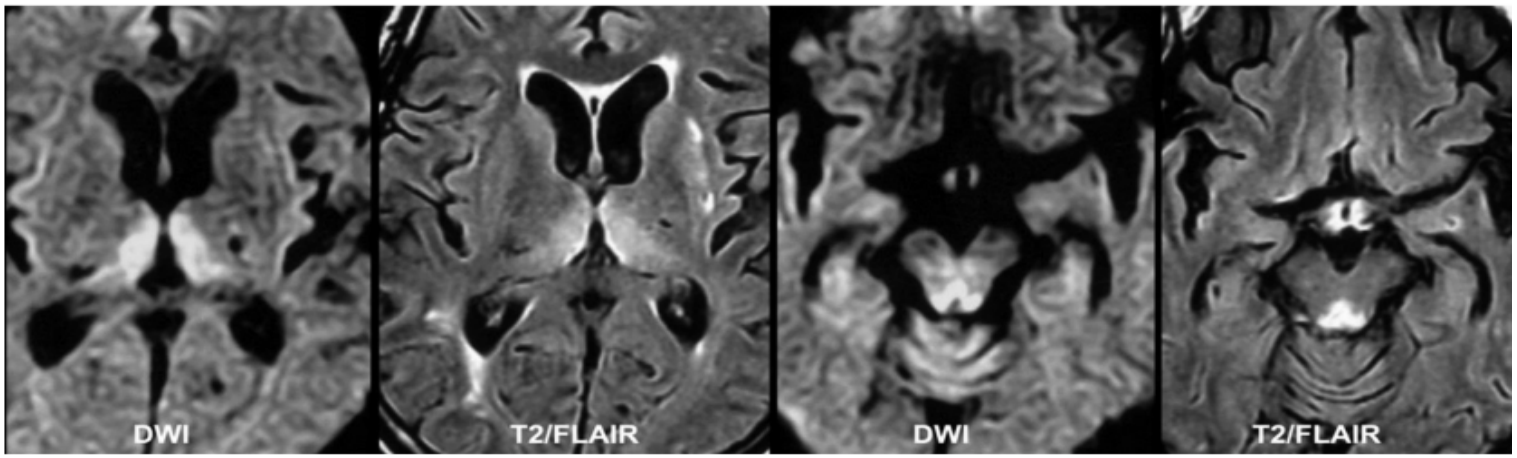
Its early recognition and aggressive blood pressure control are crucial to preventing permanent neurological deficits



Wernicke's encephalopathy

This is a particularly challenging clinical diagnosis, since encephalopathy can have many causes in haemodialysis patients (eg, hypertensive encephalopathy, drug toxicity, electrolyte and metabolic derangement and dialysis encephalopathy).

Wernicke's encephalopathy arises through a combination of poor nutritional state (common in dialysis patients) and increased loss of water-soluble vitamins during haemodialysis.



Although classically characterized by the triad of confusion, ataxia and ophthalmoplegia, patients may develop atypical features such as chorea, peripheral neuropathy and myoclonus.*

One study of ESRD patients with unexplained encephalopathy in the ICU, 40% of whom were intubated, found significantly lower thiamine evels compared to control ESRD patients.**

There is no widely available biochemical assay to aid diagnosis, so clinicians should always consider this reversible condition in patients undergoing dialysis, and treat empirically with parenteral vitamin replacement if in any doubt.

*Beal MF MJ. Nutritional and metabolic diseases of the nervous system. In: Harrison's Principles of Internal Medicine: Mc Graw Hill, 1998:2451–7.

**Hung SC, Hung SH, Tarng DC, Yang WC, Chen TW, Huang TP. Thiamine deficiency and unexplained encephalopathy in hemodialysis and peritoneal dialysis patients. Am J Kidney Dis 2001;38(5):941-947

Haemodialysis headache

This transient headache—probably related to intradialytic hypotension and changes in serum urea and magnesium concentrations—develops in about 5% of haemodialysis patients, typically towards the end of haemodialysis sessions.

It is usually a bilateral throbbing or non-pulsating headache that lasts less than 4hours.

Diagnostic criteria (international headache classification system) include >2 episodes of acute headache with each episode developing during a dialysis session, worsening headache during dialysis and headache resolution within 72hours of completing dialysis. Following successful renal transplantation, the headache must completely cease.

There are few studies to support specific treatments. ACE inhibitors and magnesium supplementation may be potential treatments.*

* Evans RW, Antoniazzi AL, Bigal ME. Expert opinion: Headaches and hemodialysis. Headache 2009;49:463–6.

Drug toxicity

Drug toxicity is one of the most common causes of neurological problems in patients with renal failure (predialysis and dialysis).

This occurs particularly with penicillins, ciprofloxacin, acyclovir, gabapentin pregabalin, benzodiazepines and opioids, since these drugs (and often thei active metabolites) are renally excreted and poorly removed by dialysis, particularly if protein bound.

For these drugs, dose adjustments are often made by reducing the dose, increasing the interval between doses or both

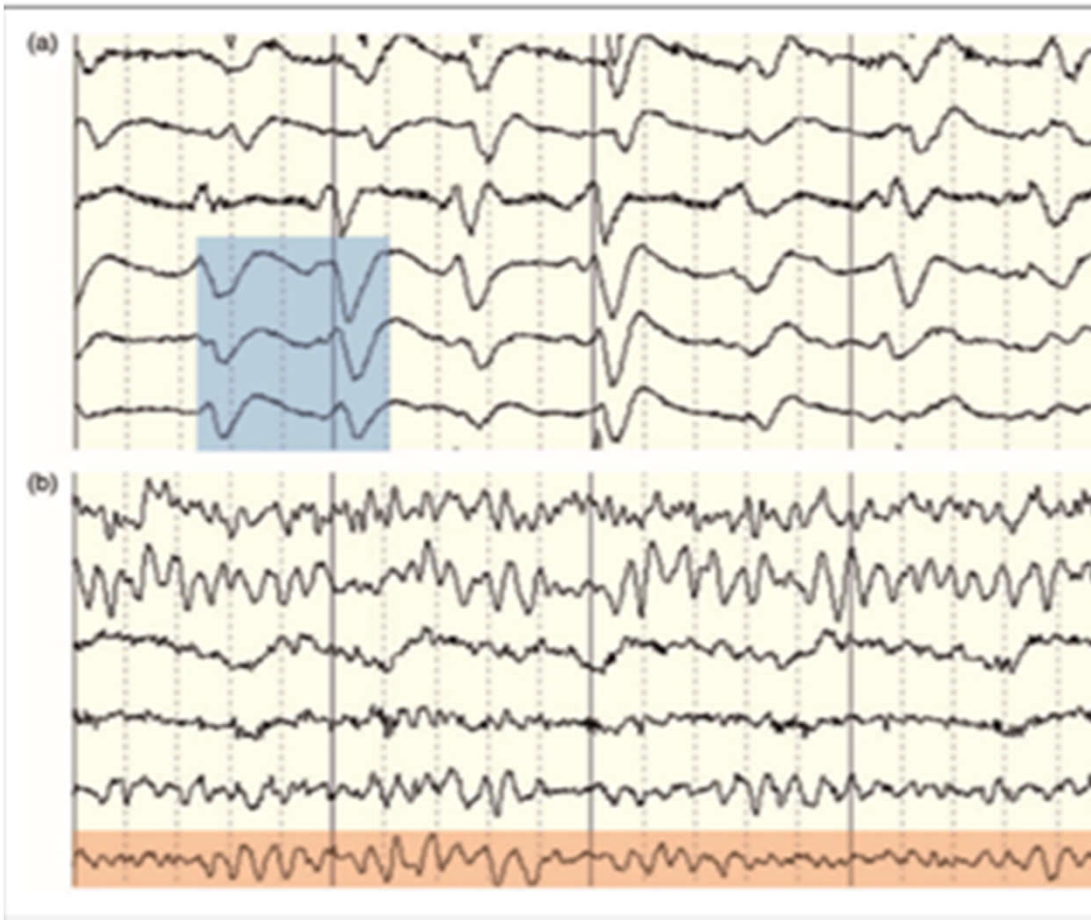
There are many accessible reference sources for dose adjustments in renal failure. For example, the Renal Dosing Database (http://www. globalrph.com/index_renal.htm) provides guidance for both renal (based on creatinine clearance) and haemodialysis dosing.

Diagnosis and management

- The first step in the treatment of uraemic encephalopathy is to identify the underlying metabolic disturbance.
- Laboratory blood tests should be undertaken and include a complete blood count, electrolyte panel, glucose, urea, creatinine, vitamin B12, folic acid, thyroid function, liver enzymes and ammonia.
- EEG findings can be of diagnostic value as the degree of EEG changes correlate with severity of encephalopathy
- Cerebral imaging with CT or MRI is required to exclude a space-occupying lesion, haemorrhage or ischaemic stroke.
- It may be necessary to conduct a lumbar puncture if the patient becomes febrile to investigate the possibility of meningitis or encephalitis

The typical features of an EEG in uraemic neuropathy are often non-specific such as a slowing of the alpha rhythm with excess delta and theta waves.

The presence of triphasic sharp waves on EEG is considered a specific feature of metabolic encephalopathies



Treatment of uremic convulsion

Seizures in patients with CKD are common and contribute to encephalopathy. It is estimated that 10% percent of patients with CKD will have a seizure at some point

Plasma protein binding and renal exertion reduced and dialysis may remove drugs

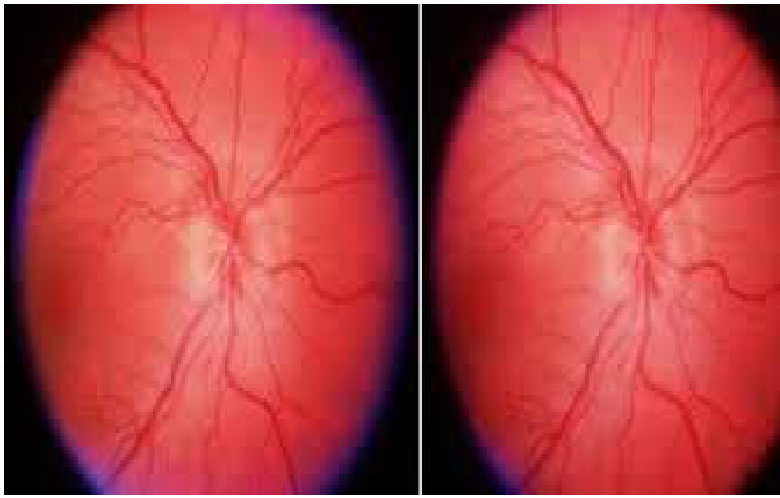
- Phenytoin
- Valporic acid
- Carbamazepine

Hemodialysis necessitate additional doses of Levetiracetam, gabapentin, topiramate, pregabalin

Anterior ischaemic optic neuropathy

Anterior ischaemic optic neuropathy can develop during haemodialysis through vascular compromise to the prelaminar optic nerve.

Additional risk factors include co-existing anaemia and dialysis-induced hypotension*



*Basile C, Addabbo G, Montanaro A. Anterior ischemic optic neuropathy and dialysis: role of hypotension and anemia. J Nephrol 2001;14:420–3.

Peripheral nervous system

Case3.

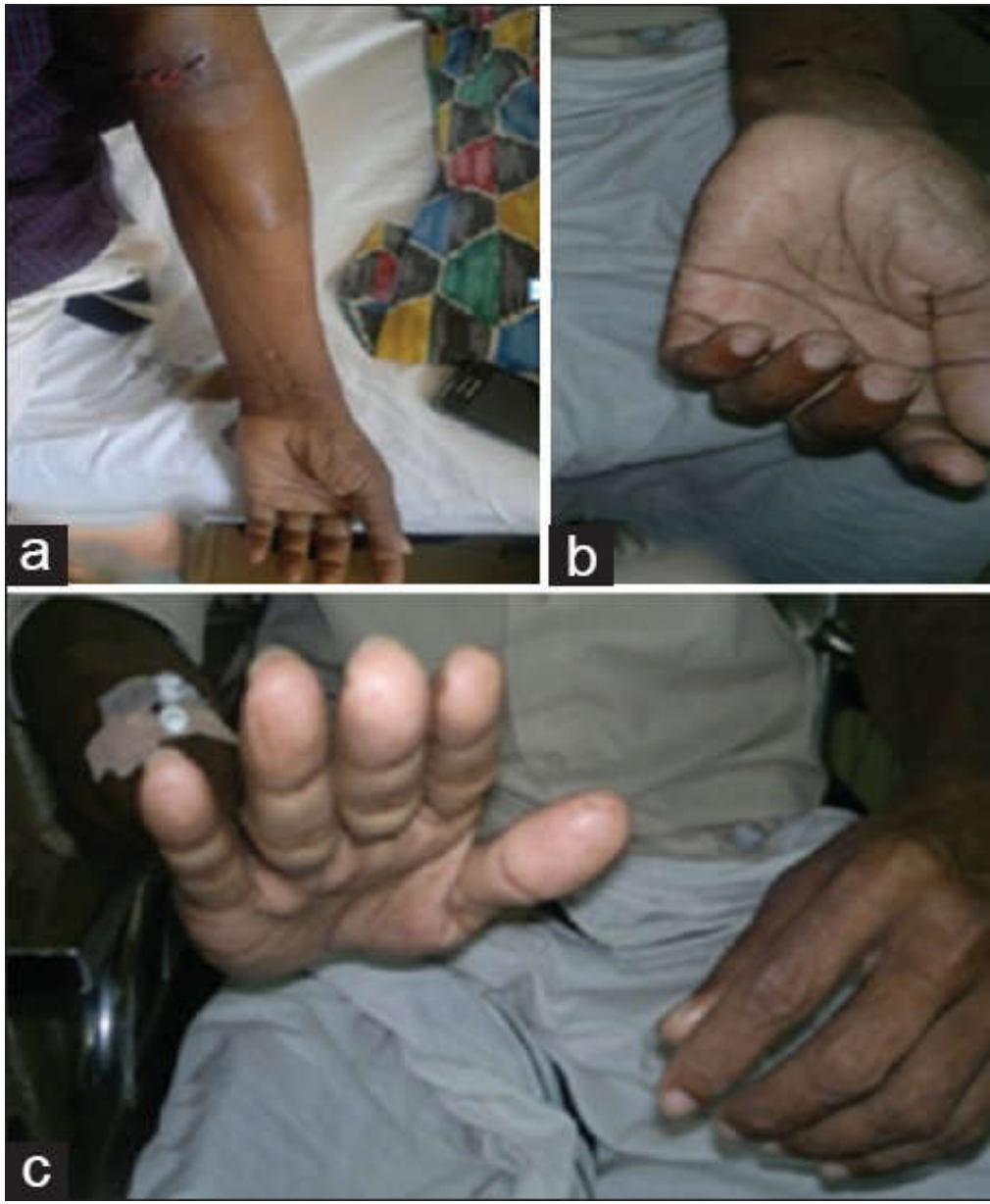
A 62-year-old male with a history of long-standing Type 2 diabetes mellitus was diagnosed to have chronic kidney disease 2 months back.

A brachiocephalic AV fistula was created on the left side for being initiated on hemodialysis.

Soon after the procedure, he developed numbness in his left hand and was unable to move the fingers of his left hand.

His left radial pulse was well palpable.

clinical examination, he was unable
flex or extend his left wrist and was
able to flex or extend the fingers of
left hand, with sensory loss over
dorsum and palmar aspect of the
hand, suggestive of radial, median,
d ulnar nerve palsy on the left side.
rve conduction study was done,
d the left median, radial and ulnar
rves were not stimulatable.



Diagnosis?

Vascular access-related nerve injury

Surgical nerve injury related to arteriovenous fistulae can occur immediately postoperatively or in the long term.

The proximity of the median nerve to the brachial artery makes it susceptible during formation of brachio-cephalic fistulae.

Disabling median nerve compression may result from a haematoma and pseudoaneurysm formation relating to surgery.

Arteriovenous fistula surgery may lead to ischaemic neuropathy of the median nerve in 1%–10% of cases.

It is probably a ‘steal’ phenomenon, where the vascular access site depletes blood supply to the distal nerve causing axonal loss.*

Additional risk factors include diabetes and severe peripheral vascular disease. If diagnosed, it is essential to re-establish distal perfusion without delay; this may require closure of the arteriovenous fistula.

*Thermann F, Kornhuber M. Ischemic monomelic neuropathy: a rare but important complication after hemodialysis access placement-a review. J Vasc Access 2011;12:113–9.

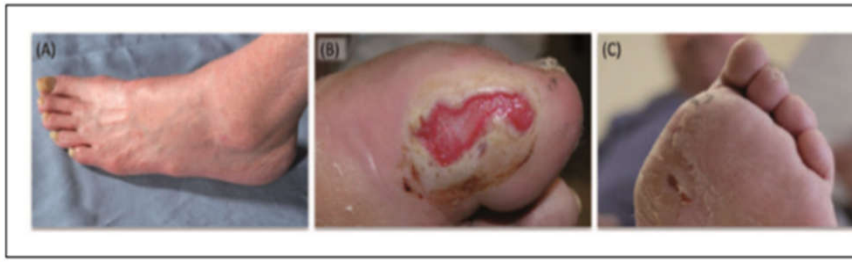
Carpal tunnel syndrome

The factors implicated include local amyloid deposition, venous hypertension distal to the arteriovenous fistula, uraemic damage to median nerve and increased extracellular volume leading to nerve ischaemia.

Studies looking at the results of surgical treatment suggest that dialysis-related carpal tunnel syndrome has a higher risk of recurrence, more postoperative complications and a slower recovery, compared with idiopathic carpal tunnel syndrome.

Kang HJ, Koh IH, Lee WY, et al. Does carpal tunnel release provide long-term relief in patients with hemodialysis-associated carpal tunnel syndrome? Clin Orthop Relat Res 2012;470:2561–5.

Peripheral neuropathy



Peripheral neuropathy in CKD, also known as uraemic neuropathy, is the most common neurological complication of CKD and affects 50-90% of dialysis patients

Unfortunately, haemodialysis itself rarely improves the neuropathy.

In milder forms, patients usually report distal paresthesia predominantly affecting the lower limbs, and on examination have loss of vibration sense and absent ankle reflexes. More severe forms can present with weakness.

Neurophysiology typically shows a length-dependent predominantly axona mixed sensory motor neuropathy

In addition to the damage of large motor and sensory fibers in uraemic neuropathy, small fiber neuropathy may also occur(Autonomic neuropathy

Research has recently demonstrated that hyperkalaemia has a pivotal role in uraemic neuropathy.

These studies provided evidence that hyperkalaemia impairs nerve function in a dose-dependent manner and this dysfunction can be normalised with the removal of excess serum potassium.

These studies also suggest that maintaining normal levels of potassium in CKD patients may prevent peripheral nerve injury.*

*Arnold R, Pussell BA, Howells J, et al. Evidence for a causal relationship between hyperkalaemia and axonal ysfunction in end-stage kidney disease. Clin Neurophysiol 2014; 125: 179–185.

Diagnosis and management.

The gold standard for diagnosis of neuropathy is clinical neurological examination including nerve conduction studies

Clinical diagnosis of neuropathy in CKD requires eliminating other causes of neuropathy such as glucose dysmetabolism and connective tissue disease (DM, vasculitis, CIDP)

similar symptoms with an acute onset or rapid progression may indicate a different causality such as Guillian Barre Syndrome or vasculitic neuropathy

Treatment

Haemodiafiltration

Renal transplantation

Normal levels of potassium

Tricyclic antidepressants and anticonvulsants (Anticonvulsants such as pregabalin or gabapentin have dosing restrictions in patients according to creatinine clearance)

Dialysis-induced hypotension

Symptomatic hypotension is a common intradialytic complication, and increasingly recognized as a serious problem with the increasing number of elderly and diabetic patients undergoing hemodialysis.

It can cause cerebral hypo perfusion and ischemia.

Risk factors in addition to rapid ultrafiltration include cardiovascular risks.

Best management includes close supervision and monitoring by dialysis staff and pharmacological management of co-existing cardiovascular and autonomic neuropathy*

*Sułowicz W, Radziszewski A. Dialysis induced hypotension–a serious clinical problem in renal replacement therapy. Med Pregl 2007;60(Suppl 2):14–20.

Myopathy

Approximately 50% of CKD patients on dialysis are affected by myopathy.

Myopathy is characterised by proximal muscle weakness in the muscles of the lower limbs.

Possible aetiologies of myopathy include hyperparathyroidism, metabolic bone disease with vitamin D deficiency, impaired potassium regulation, accumulation of uraemic toxins and carnitine deficiency.

Diagnosis and management.

No diagnostic tool or biochemical parameter can be used to diagnose uraemic myopathy and electromyography as well as levels of muscle enzymes are typically normal in these patients.

However, demonstration of weakness in proximal pelvic muscles is a strong indicator of myopathy.

Muscle biopsy studies have shown atrophy of type II fibres and fibre splitting,but biopsy is rarely undertaken due to the invasive nature of the procedure.

No specific treatment exists for uraemic myopathy however management of the potential contributing factors such as hyperparathyroidism, vitamin D and anaemia may be beneficial.

Table 5 Neurological investigations in renal dialysis and transplant patients

Investigations	Indication
Imaging	
CT scan of head MR scan of brain	Unwell patient in acute setting Stroke Suspected CNS infections or focal lesion Encephalopathy Primary CNS malignancy
Doppler ultrasound scan	Suspected ischaemic neuropathy
Electrophysiological tests	
Electroencephalogram	Encephalopathy Episodic confusion
Nerve conduction studies	Suspected mononeuropathy or polyneuropathy Fatiguable weakness (repetitive nerve stimulation)
Electromyography	Suspected myopathy or neuromuscular junction pathology

Key points

- Neurological complications are highly prevalent in CKD and are a major cause of morbidity and mortality.
- Presentations of altered mental status may be differentiated according to acute vs. chronic CNS derangements.
- Physical disability in CKD is highly prevalent most commonly caused by peripheral neuropathy, autonomic neuropathy and myopathy.

Thanks for your attention