Neurology and renal disorders

Osheik Seidi MBBS ABIM MRCP(UK), Consultant Neurologist, *Sunderland Royal Hospital and the Regional Neuroscience Centre, Newcastle upon Tyne*

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Following the introduction of haemodialysis and renal transplantation it became particularly clear that renal disease may adversely affect the nervous system. A range of neurological manifestations of acute (ARF) and chronic renal failure (CRF) have been recognised.

- There are well-known interactions when systemic disorders such as diabetes or hypertension affect both the kidney and the nervous system.
- Systemic lupus erythematosus (SLE), other vasculitides and granulomatous disorders commonly show neurological and renal complications.
- Electrolyte disturbances in patients with renal and systemic disorders can manifest with specific and non-specific neurological features. These should be recognised early to avoid permanent sequelae which may occur if not treated promptly, as in the osmotic demyelination syndromes following rapid correction of hypo- or hypernatraemia.
- Rare, but potentially treatable, serious neurorenal conditions include thrombotic thrombocytopenic purpura (TTP) and cocaine-related vasculitis.[1]
- Neurological features may be the first indication of renal disease, for example peripheral neuropathy with CRF, aneurysmal subarachnoid haemorrhage in polycystic kidney disease (PKD), myoclonus in ARF or confusion and coma in ARF or CRF.

This review summarises some of these conditions in which neurological manifestations are seen in connection with renal disorders.

Neurological problems associated with renal replacement therapies

Dialysis dysequilibrium syndrome

The dialysis dysequilibrium syndrome is a complication of haemodialysis caused by the creation of an osmotic gradient between the brain cells and the plasma. Rapid clearance of urea and other solutes leads to a shift of water into the brain parenchyma with resultant cerebral oedema. It presents with headache, nausea, vomiting, restlessness, muscle cramps and confusion. It usually resolves in a few hours after dialysis and is prevented by slower dialysis.

Dialysis dementia

Dialysis dementia is now seen infrequently (if at all) compared with the early years of haemodialysis. It was linked to an increased level of aluminium in the soft water used in the dialysate and presented with dysarthria, dysphasia and dysgraphia, progressing to gait apraxia, myoclonic jerks and seizures, leading in extreme cases to immobility and mutism followed by death. Dialysis dementia is treated with the chelating agent desferrioxamine.[2]

Uraemic encephalopathy

Either acute or chronic, uraemic encephalopathy is usually more severe in the context of ARF. The initial symptoms are fatigue, poor concentration and clumsiness, but as the renal function deteriorates there is progression to asterixis, multifocal mycoclonic jerks, generalised seizures, confusion and coma. In the chronic form, patients show emotional lability, sluggishness and inversion of sleep pattern as well as frontal lobe features, including impaired abstract thinking, palmomental reflex and a resistance to passive movement (paratonia). The correlation is poor between the chronic form and the degree of uraemia. Both forms improve with renal replacement therapies (RRTs) and may resolve completely after successful renal transplantation.[3]

Osmotic demyelination syndromes

The osmotic demyelination syndromes (ODS) complicate treatment of hyponatraemia in which serum sodium is usually less than 120 mmol/l. The commonly recognised type is central pontine myelinolysis (CPM), although extrapontine myelinolysis (EPM) is increasingly reported; the pathogenesis is the same in both types. ODS should be considered in patients who deteriorate neurologically after an illness associated with hyponatraemia or have received a large volume of intravenous fluids even if the imaging is not supportive initially. To prevent this serious complication the sodium should not be corrected by more than 8 mmol/l/day, particularly in chronic hyponatraemia (serum sodium <136 mmol/l for >48 hours).

CPM presents with brainstem dysfunction, including flaccid tetraparesis and occasionally the locked-in syndrome. EPM has variable presentations which depend on the affected area

Key Points

The kidney and the nervous system have close interactions under both physiological and pathological states

Systemic disorders like diabetes, hypertension, vasculitudes and genetic disorders can affect both the nervous system and the kidney

Awareness and early recognition of conditions such as thrombocytopenic purpura and osmotic demyelination syndromes should lead to prompt treatment and prevention of serious sequelae

Neurological features can be the first manifestations of a renal disease or complications of renal replacement therapies

KEY WORDS: brain, dialysis, genetic disorders, kidney, muscle diseases, neurological manifestations, neurorenal, renal, vascular disorders

and may cause parkinsonism, confusion, hemiparesis and hemianaesthesia.[4] The clinical picture can evolve over several days. Magnetic resonance imaging is usually diagnostic in CPM, showing focal demyelination in the basis pontis (Fig 1).

Treatment is supportive and the prognosis is variable but has greatly improved with early intervention.[5] Careful management of hyponatraemia is vital in prevention. ODS has also been reported with rapid correction of hypernatraemia, but this is less well defined. In a few cases ODS has been attributed to severe hypophosphataemia.[6]

Neurological complications of renal transplantation

These are summarised in Table 1.

Peripheral nerve problems in renal disease

There is a wide range of peripheral nerve complications in renal disease but sensorimotor neuropathy or pressure palsies are the most common. A frequent presenting symptom is distal pain due to small fibre sensory neuropathy; this can be the first manifestation of CRF. On the background of neuropathy the nerves may be more liable to pressure palsies. Carpal tunnel syndrome is particularly common in patients with CRF, even if they do not have a dialysis fistula in a forearm,[7] and in some cases there is coexistence of dialysis amyloid which affects both wrists.[8]

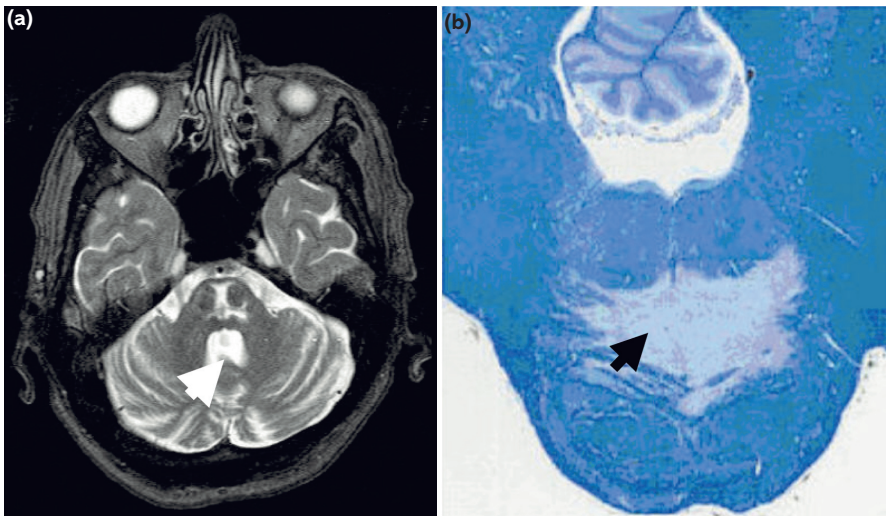

Fig 1. T2-weighted magnetic resonance image showing (a) central pontine myelinolysis (CPM) (white arrow) and (b) a myelin stained cross-section of the pons showing CPM in the basis pontis (black arrow) in a different patient.[4] Reproduced by kind permission of BMJ Publishing Group Ltd.

Table 1. Neurological complications of renal transplantation.

	Complications
Surgical procedure	• Peripheral nerve injury: mostly neuropraxia of femoral or lateral cutaneous nerve of thigh • Conus medullaris syndrome/spinal cord ischaemia secondary to diversion of blood in the iliac vessels to the grafted kidney
Immunosuppression	• Acute hypertension (ciclosporin or tacrolimus) • Reversible posterior leukoencephalopathy • CNS infections: – viral (eg CMV, *Herpes zoster*, EBV (rarely JCV), leading to progressive multifocal leukoencephalopathy – *Mycobacterium tuberculosis*: meningitis – *Listeria monocytogenes*: meningitis, rhombencephalitis – cryptococcal or nocardia meningitis • Post-transplant lymphoproliferative disorder: – ranges from mild B cell proliferation to malignant primary CNS lymphoma

CMV = cytomegalovirus; CNS = central nervous system; EBV = Epstein-Barr virus; JCV = Jamestown-Canyon virus.

Systemic disorders with neurorenal manifestations

Hypertension and diabetes are beyond the scope of this article.

Thrombotic thrombocytopenic purpura

The first description of TTP was in Russia in 1924 in a young woman with an abrupt onset of haemolytic anaemia, thrombocytopenia, neurological manifestations, renal dysfunction and fever.[9] Deficiency of the metalloprotease ADAMTS-13 (A Disintegrin-like and Metalloprotease with Thrombospondin Motifs) is the major risk factor. Endothelial cells secrete adhesive and unusually large von Willebrand factor multimers which are normally cleaved by ADAMTS-13. Deficiency of the protease causes platelet microthrombi showers into any vascular bed and the occlusive microangiopathy characteristic of TTP.[10] The clinical and neurological features are shown in Tables 2 and 3.

Vasculitides and granulomatous disorders

The primary vasculitides (polyarteritis nodosa, SLE and Churg-Strauss disease) have protean neurological and renal manifestations, the former including encephalopathy, seizures, mononeuritis multiplex, peripheral neuropathy and stroke.

Secondary vasculitides involving the kidney and the nervous system are associated with infections (eg infective endocarditis), toxins and illicit drug use, and in association with lymphoproliferative disorders. Granulomatous disorders, particularly Wegener's granulomatosis, can manifest with renal involvement in association with cranial nerve and peripheral neuropathies as well as

Table 2. Clinical features of thrombotic thrombocytopenic purpura (TTP).

Characteristic features include:	• Thrombocytopenia: petechia • Fever (60%) • Microscopic haematuria (gross in 18%) • Neurological deficit • Microangiopathic haemolytic anaemia
Other important facts:	• TTP can affect any organ system • TTP is a potentially treatable life-threatening multisystem disease • Non-specific flu-like symptoms are prodromal • It is unusual for all features to be present from the outset • A high index of suspicion is necessary • Coomb's test is negative, clotting screen is normal, lactate dehydrogenase is high • Treatment is plasma exchange (usually 5–10 sessions) with adequate general support

Table 3. Neurological manifestations of thrombotic thrombocytopenic purpura (TTP).

- Altered mental status (36%):
  - agitation (very common)
  - confusion
  - coma (the level may fluctuate secondary to the microhaemorrhagic and microocclusive vascular changes in the brain)
- Generalised headache
- Focal defects:
  - hemiplegia (12%)
- Visual disturbance
- Seizures (16%)
- Paraesthesia (4%)
- Cerebral bleeding (an ominous feature)

focal central nervous system (CNS) ischaemia.[3]

Genetic disorders involving the nervous system and the kidney

Polycystic kidney disease

PKD is due to a defect in polycystin, a membrane glycoprotein. Renal and liver cysts may be associated with intracranial aneurysm, hypertension and cardiac valvular defects. This genetically heterogeneous group of disorders is usually autosomal dominant (ADPKD) and the defect in most Europeans is mapped to chromosome 16p13.3 (ADPKD-1).

Intracranial aneurysm is seen in 5–15%,[11] but the pathological link between PKD and intracranial aneurysm is as yet unknown. There is no correlation between the presence of intracranial aneurysm and hypertension. It is recommended to screen patients with adult PKD and a family history of intracranial aneurysm by means of magnetic resonance angiography,[12] which is non-invasive and has a sensitivity of 85% and specificity of 90%.[13]

PKD is also associated with an increased incidence of mitral and aortic valve regurgitation as well as mitral valve prolapse, leading to increased risk of embolic strokes in young patients.

von Hippel-Lindau disease

The defect in the autosomal dominant disorder von Hippel-Lindau (VHL) disease is mapped to chromosome 3p25-p26 and causes dysfunction in a tumour suppressor gene leading to an increased risk of developing various tumours. CNS haemangioblastomas are important, predominantly in the cerebellum (Fig 2), less commonly in the spinal cord. Renal cell carcinomas are the major cause of death. Ocular presentations are common since retinal capillary haemangioma is a frequent manifestation of VHL disease.[14]

Fabry's disease (angiokeratoma corporis diffusum)

Deficiency of the lysosomal enzyme α-galactosidase A (ceramide trihexosidase) leads to the accumulation of glycosphingolipids in the small blood vessels in the brain, peripheral nerves, myocardium, kidney, cornea and the skin. This results in hypertension, renal and heart failure, as well as lancinating acral pains, cerebral vasculopathy, dysautonomia and characteristic skin lesions (angiokeratomas).[15] Fabry's disease is X linked and multiple mutations are identified, the commonest being Xq22. Recently, enzyme replacement therapy has been introduced with good results,[16] and experimental gene transfer therapy is under investigation.[17]

Tuberous sclerosis

The most common neurocutaneous syndrome after neurofibromatosis, tuberous sclerosis (TS), causes epilepsy, mental retardation, and the characteristic skin lesions of adenoma sebaceum. Renal involvement is seen in 40–80% of cases, with the development of epithelial cysts leading to haematuria and recurrent upper urinary tract infections. There is a tendency to develop angiomyolipomata. TS is autosomal dominant, with almost complete penetrance but a wide range of clinical severity and new mutations are also seen. It is mapped to chromosomes 9 (TSC1 gene at 9q34) and 16 (TSC2 at 16p13.3).

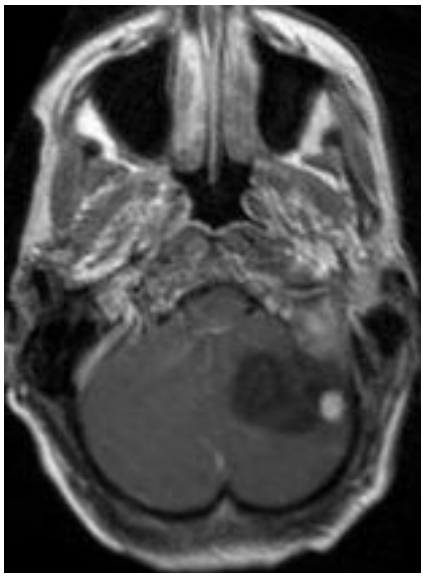

Fig 2. T1-weighted gadolinium enhanced brain magnetic resonance image. Axial section, through the posterior fossa showing a cerebellar haemangioblastoma. Courtesy of Dr Jay Krishnan, Department of Neuroradiology, Newcastle General Hospital.

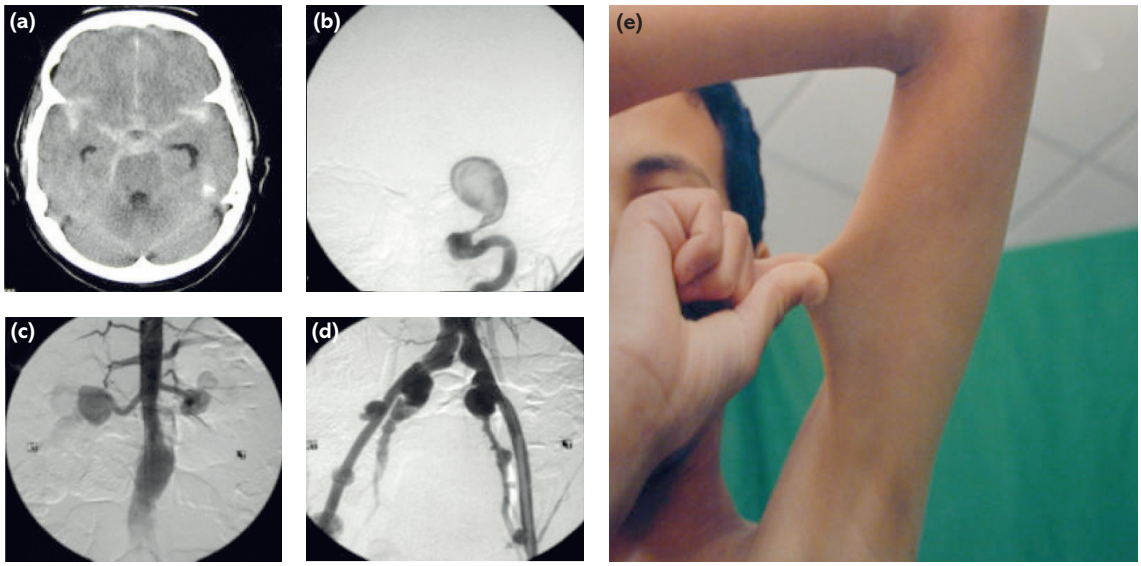

Fig 3. A 26-year-old man with Ehlers-Danlos syndrome who presented with repeated renal infarction and an episode of subarachnoid haemorrhage (SAH).
(a) SAH shown in plain CT scan. He has large cerebral (b), bilateral renal (c) and multiple iliac arterial (d) aneurysms. He has very elastic skin with hyperextensible joints (e). Courtesy of Dr V Jayakrishnan, Department of Neuroradiology, Newcastle General Hospital.

Disorders of blood vessel walls affecting the central nervous system and the kidney

Ehlers-Danlos syndrome

The Ehlers-Danlos syndrome encompasses a heterogeneous group of disorders of the connective tissue, usually recessively inherited and involving different components of collagen. It can cause cerebral and renal artery aneurysms, leading to subarachnoid haemorrhage (Fig 3) and renal infarction.[18]

Fibromuscular dysplasia

Of unknown aetiology, fibromuscular dysplasia (FMD) affects the renal arteries in 85% of patients and often presents with renovascular hypertension. The internal carotid arteries are the second most commonly affected and are involved bilaterally in about 65% leading to transient ischaemic attack (29%) or thromboembolic stroke (6%). FMD has been associated with intracranial aneurysm in as many as 30% of patients and spontaneous carotid artery dissection in 10–20%. About 30% of those with carotid FMD also have renal artery FMD and 10% have vertebral artery involvement. FMD may also affect lumbar, mesenteric, coeliac, hepatic and iliac arteries. There is a weak association with α-1 antitrypsin deficiency and suspicion of hormonal involvement in this predominantly female disease.

Renal arteriography may help in confirming the diagnosis. FMD has three distinct histological types: intimal, medial and subadventitial (perimedial) fibroplasia of the arterial wall. The medial type is the most common, classically diagnosed on angiography by the presence of a 'string of beads' appearance due to the presence of luminal stenosis alternating with aneurysmal outpouchings. Percutaneous transluminal renal angioplasty may resolve renovascular hypertension and reduce the risk of stroke.[19]

Muscle and the kidney

Rhabdomyolysis

Because of disruption of the muscle sarcolemma with fibre necrosis (Fig 4), leading to the spillage of muscle contents

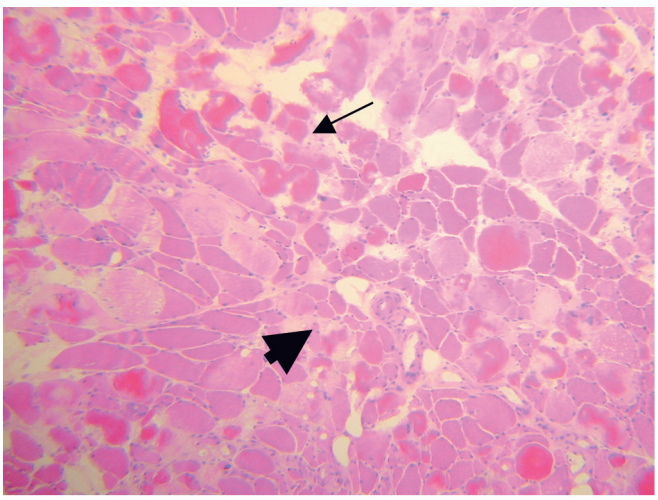

Fig 4. A muscle photomicrograph (x 300) stained with haematoxylin/eosin, showing fibre necrosis (thin arrow) and widespread disruption of the sarcolemma (thick arrow) typical of rhabdomyolysis. Courtesy of Dr J Miller, Newcastle General Hospital.

Fig 5. Urine sample showing (a) myoglobinuria in contrast to (b) normal urine.

into the circulation, there is a triad of myalgia, muscle weakness and the dark urine of myoglobinuria (Fig 5). The most serious complication is ARF. Despite the dark brown or red discolouration of the urine, microscopy does not show red cells (Table 4). Numerous disorders may cause rhabdomyolysis leading to myoglobinuria (Table 5).[20]

Uraemic myopathy

Uraemic myopathy is a controversial disorder reputed to cause wasting of proximal muscles with normal creatinine kinase. Muscle biopsy reveals loss of type 2 fibres. Most cases improve with adequate RRT. There is frequently associated bone pain and muscle tenderness and a suspected link with osteomalacia and hyperparathyroidism.[21]

Table 4. Action in patients with dark red urine.

- A positive urine dipstick for blood (haem) should be followed by microscopy without delay
- If no red cells are seen, consider myoglobinuria and haemoglobinuria*
- Myoglobinuria is serious and can lead to acute renal failure
- There are many causes of rhabdomyolysis and a careful differential needs early consideration
- A muscle biopsy may help in the diagnosis**

* Fig 5; ** Fig 4.

Table 5. Causes of rhabdomyolysis.

Muscle diseases	
Genetic	• Glycogen and fat oxidation pathway defects (eg McArdle disease and carnitine palmitoyl transferase I & II, respectively) • Malignant hyperpyrexia
Secondary	• Drugs: – eg statins • Neuroleptic malignant syndrome: – chlorpromazine and other phenothiazines, rapid withdrawal of dopamine agonists • Heat stroke • Mechanical: – crush injuries (compartment syndromes) – status epilepticus • Venoms: – snake bites • Inflammatory: – autoimmune (polymyositis) – infections (legionella, influenza A, B) • Endocrine and metabolic: – thyroid disease – severe hypophosphataemia

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Drug-induced disorders of the nervous system

Mark R Baker MA MB BChir PhD MRCP, Specialist Registrar, *Department of Neurology, Royal Victoria Infirmary, Newcastle upon Tyne*

Don J Mahad MB ChB PhD MRCP, Specialist Registrar and Wellcome Trust Intermediate Fellow, *Mitochondrial Research Group, School of Neurology, Neurobiology and Psychiatry, Medical School, Newcastle upon Tyne*

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Drug-induced neurological disorders (DINDs) are important because early recognition and drug withdrawal can prevent irreversible damage. This review deals specifically with the recognised neurological complications of prescription-only, single-agent therapy, either at recommended doses or in excess (including overdose and abuse of prescription drugs), and summarises the more important DINDs. Some of the drugs described may also exacerbate neurological disorders that are often subclinical and undiagnosed. Drug interactions can increase the toxicity of single agents; these are well documented elsewhere.[1]

DINDs can occur at initiation, during sudden withdrawal of therapy (eg tramadol withdrawal seizures) and after many months or years of therapy (eg valproate encephalopathy). Treatment is primarily concerned with controlled withdrawal, but toxic levels may necessitate haemodialysis or haemofiltration (eg lithium), specific neutralising therapies (eg Fab fragments in digoxin toxicity) or symptomatic treatments.

Recent detailed and comprehensive reviews of DINDs can be found elsewhere.[2,3]

Seizures

Seizures may be caused by antipsychotics, antidepressants, antineoplastic agents (alkylators, antimetabolites, vinca alkaloids, ifosfamide and cisplatin), penicillins, cephalosporins, quinolones, antimalarials, aminophylline and allopurinol. They are frequently observed in drug-induced encephalopathy (see below). Other less frequently reported drugs which may induce seizures include

Key Points

- **Prescription drugs are an important reversible cause of common neurological disorders**
- **Mitochondrial toxicity is an important mechanism in a number of drug-induced neurological disorders (DINDs)**
- **Early recognition of DINDs and drug withdrawal can prevent irreversible damage**
- **Some DINDs require urgent symptomatic treatment to avoid serious complications**
- **Vitamins and essential trace elements may help to reverse some DINDs**
- **Statin-induced neurological disorders are likely to become more prevalent**
- **Increasing use of novel humanised monoclonal antibodies may cause previously unrecognised DINDs**

KEY WORDS: antiretrovirals, drug-induced disorders, mitochondrion, monoclonal antibodies, nervous system, statins