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The nature, consequences, and management of neurological disorders in chronic kidney disease

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Abstract

Perhaps no other organ in the body is affected as often and in as many ways as the brain is in patients with chronic kidney disease (CKD). Several factors contribute to the neurological disorders in CKD including accumulation of uremic toxins, metabolic and hemodynamic disorders, oxidative stress, inflammation, and impaired blood brain barrier among others. The neurological disorders in CKD involve both peripheral and central nervous system. The peripheral neurological symptoms of CKD are due to somatic and cranial peripheral neuropathies as well as a myopathy. The central neurological symptoms of CKD are due to the cortical predominantly cortical, or subcortical lesions. Cognitive decline, encephalopathy, cortical myoclonus, asterixis and epileptic seizures are distinct features of the cortical disorders of CKD. Diffuse white matter disease due to ischemia and hypoxia may be an important cause of subcortical encephalopathy. A special and more benign form of subcortical disorder caused by brain edema in CKD is termed posterior reversible encephalopathy. Subcortical pathology especially when it affects the basal ganglia causes a number of movement disorders including Parkinsonism, chorea and dystonia. A stimulus-sensitive reflex myoclonus is believed to originate from the medullary structures. Sleep disorder and restless leg syndrome are common in CKD and have both central and peripheral origin. This article provides an overview of the available data on the nature, prevalence, pathophysiology, consequences and treatment of neurological complications of CKD.

Key words: Chronic kidney disease, uremia, peripheral neuropathy, cognitive dysfunction, central nervous system, dementia, stroke

INTRODUCTION

Nearly 40 years have passed since the first comprehensive review of the abnormal brain symptoms of renal disease appeared in the literature.^{1,2} During the past 4 decades, our understanding of kidney dysfunction and the possible mechanisms through which it can alter the nervous

system function has improved significantly. The focus of this article is to provide an overview of the prevalence, nature, mechanisms, and consequences of the neurological disorders in chronic kidney disease (CKD).

The prevalence of CKD has been reported as 13% in the United States with a majority of patients manifesting some neurological symptom(s).³ The neurological complications of CKD can be categorized into those that pertain to the peripheral nervous system (neuropathy, myopathy) (Figure 1) and those that involve the central nervous system (CNS). The CNS complications can be further divided into cortical or predominantly cortical (Figure 2) and subcortical disorders (Figure 3).

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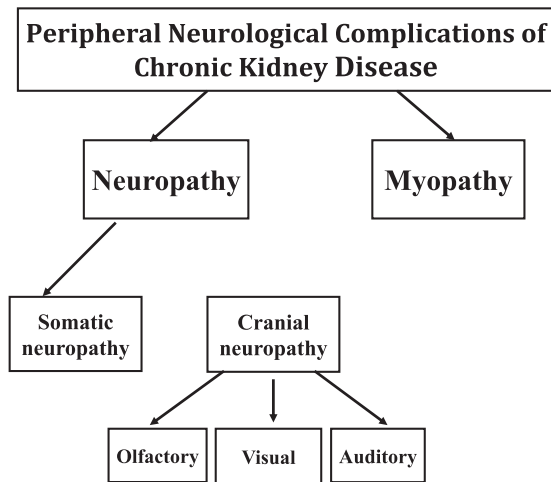


Figure 1 Peripheral Neurological Complications of Kidney Disease

PERIPHERAL NEUROLOGIC COMPLICATIONS OF CKD

Peripheral neuropathy

1-Peripheral (somatic) neuropathy

Peripheral neuropathy of the limbs has been reported in 50%–60% of patients with end stage renal disease.⁴ The prevalence of peripheral nervous system involvement in CKD may be even higher than the percentage cited above

since somatosensory evoked potentials in CKD patients with no or minimal clinical symptoms of neuropathy often shows distinct sensory conduction abnormalities.⁵ CKD induced neuropathy is progressive and involves both motor and sensory axons.⁶ Unpleasant and sometimes painful sensations, mostly affecting legs, impair patients’ daily activities, and sleep; in more advanced cases, weakness of the legs as well as poor balance severely impact patients’ quality of life.

CKD-induced peripheral neuropathy results from a variety of mechanisms. Intracellular accumulation of calcium secondary to hyperkalemia in CKD and reversal of the K/Ca pump can cause axonal damage and significant axonal depolarization (presumably caused by hyperkalemia) has been demonstrated in CKD in the early stages of neuropathy.^{6,7} Other implicated factors in CKD-induced neuropathy include the neurotoxic effects of small molecules (e.g., myoinositol and methylguanidine) which accumulate in the body fluids in CKD, increased parathyroid hormone level and vitamin B1 deficiency.⁸ Furthermore, many drugs which are used for management of CKD are capable of causing peripheral neuropathy.^{9,10}

Treatment of CKD-related peripheral neuropathy is both symptomatic and mechanistic. Painful sensations of CKD-induced neuropathy may respond partially to gabapentin and tricyclic antidepressants. However, gabapentin has been reported to induce central neurotoxicity in some CKD patients which is most likely related to the CKD-induced increased permeability of the blood-brain

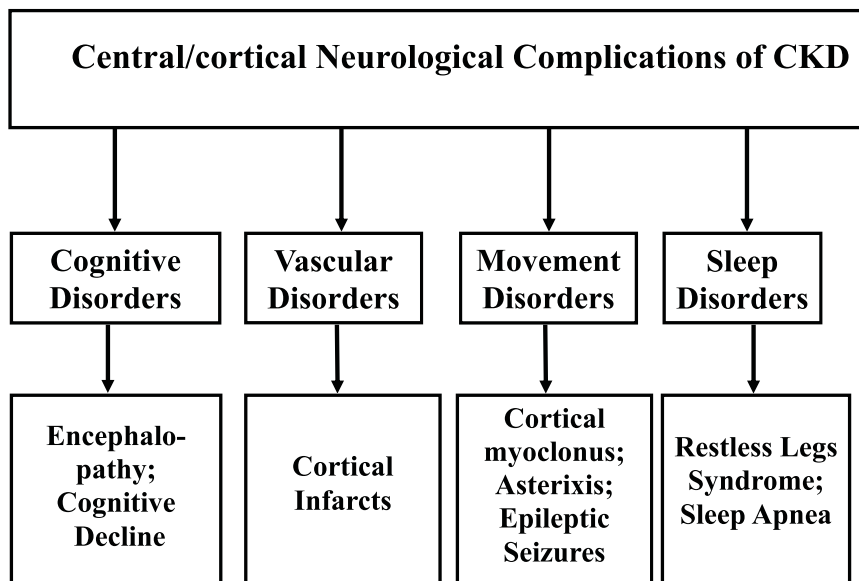


Figure 2 Central/cortical complications of CKD

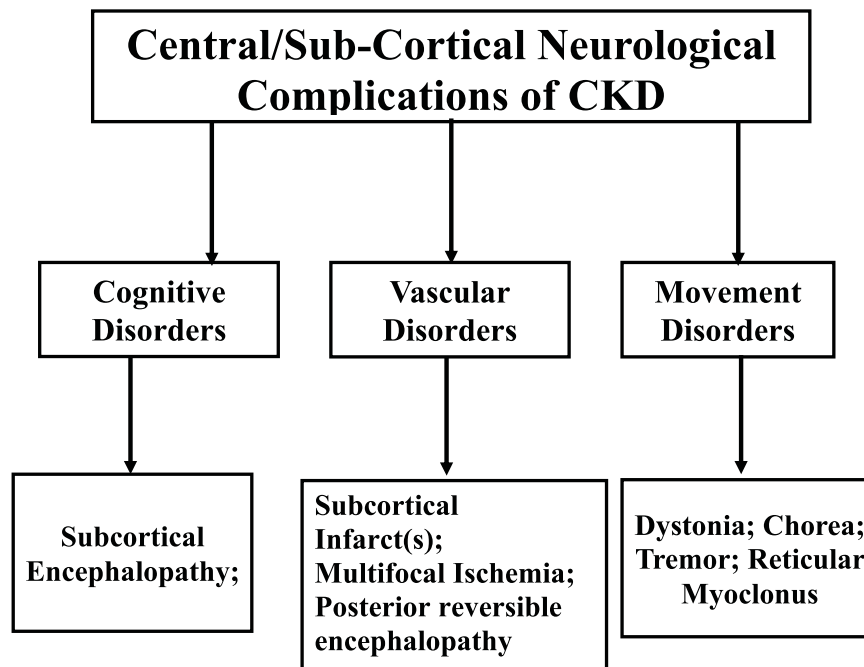


Figure 3 Central/subcortical complications of CKD

barrier and exposure of the brain to the neurotoxic effects of the drug.¹¹ The peripheral neuropathy of CKD usually does not respond to peritoneal dialysis, but in some patients improves with hemodialysis. Renal transplantation often leads to rapid reversal of neuropathic symptoms.^{11,12}

2-Cranial neuropathy

Among the cranial nerves, acoustic, and olfactory nerves are especially susceptible to the deleterious effects of uremia. In a study of 47 elderly subjects with CKD, mean auditory threshold was 15 dB higher than that of the age matched controls. A brain stem auditory evoked potential (BAEP) study showed prolongation of the I–III interpeak intervals in nearly 40% of the subjects with CKD denoting the presence of auditory neuropathy.¹³ Such BAEP abnormalities have been shown also in rats with CKD who have undergone nephrectomy.¹⁴ Other investigators^{15,16} have shown BAEP evidence for presence of additional conduction defects in the brain stem's central auditory pathways. BAEP abnormalities improved or normalized in some patients after initiation of dialysis. Mirahmadi and Vaziri,¹⁷ however, have shown that peritoneal dialysis does not improve the hearing loss of patients with chronic kidney disease.

Olfactory dysfunction is common among the patients with CKD. Griep et al.,¹⁸ studied the olfactory threshold and odor perception in 101 subjects with CKD (mean

creatinine clearance of 29.5 ml/min) and compared the results with 15 age matched healthy controls. Odor discrimination was impaired in patients with CKD compared to controls. Odor perception threshold was significantly higher in patients maintained on peritoneal dialysis and hemodialysis compared to controls. Olfaction was normal in kidney transplant patients and olfactory abnormalities in patients with end stage renal disease reverted to normal after kidney transplantation. Another study¹⁹ of 64 patients with CKD, have found normal odor perception threshold, but significantly reduced odor identification and discrimination in 56% of the CKD subjects compared to controls; olfactory abnormalities were reversed after successful renal transplantation. The mechanism of impaired olfaction is believed to be related to harmful effects of uremic toxins on olfactory lamina and olfactory bulb. By limiting the attraction to food, the impaired olfactory function may contribute to the highly prevalent anorexia and malnutrition of CKD.

Patients with CKD, usually do not have significant visual complaints, however, rare and reversible cases of uremic optic neuropathy have been reported in this population.²⁰ Several investigators have demonstrated prolongation of the major component of P100 of the visual evoked response (VEP) in dialysis-treated and untreated uremic patients.^{21,22} with restoration of VEP abnormalities to normal following kidney transplantation.²³

Uremic myopathy

A typical myopathy characterized by proximal muscle weakness, muscle atrophy, and characteristic electromyographic features of myopathy can develop in uremic patients, but its true prevalence is unknown. Uremic myopathy is uncommon in patients with GFRs of higher than 25 ml/min and is more common among females older than 60 years of age.²⁴ Several mechanisms have been proposed to explain the development of uremic myopathy: (I) Factors which increase cytosolic calcium in myocytes such as secondary hyperparathyroidism and impaired vitamin D metabolism. (II) Accumulation of intermediate molecular weight uremic toxins such as guanidine compounds and ouabain which also increase calcium influx by altering the Na-K ATPase activity. (III) Other putative factors to include mitochondrial dysfunction which manifests by quick and abnormal rise of serum lactic acid after minimal exercise²⁵ and is, in part, caused by depletion of skeletal muscle mitochondrial content,²⁶ (IV) CKD-induced insulin resistance which limits delivery of glucose for production of energy,²⁷ and (V) CKD associated anemia²⁸ which by limiting oxygen delivery contributes to the skeletal muscle atrophy and impaired exercise capacity in patients with advanced CKD. Treatment of uremic myopathy includes adequate renal replacement therapy, improved nutrition, carnitine supplementation, prevention and management of secondary hyperparathyroidism, correction of anemia with recombinant erythropoietin, and renal transplantation. The latter often improves the myopathy but fails to fully restore muscle function.

DISORDERS OF THE CENTRAL NERVOUS SYSTEM IN CKD

Cortical or predominantly cortical symptoms in CKD

The features of cortical disorder in CKD include cognitive dysfunction, delirium, encephalopathy and dementia, focal stroke-related symptoms (paralysis, spasticity) as well as cortically originated abnormal movements such as cortical myoclonus, asterixis, and epileptic seizures (Figure 2).

Impaired cognition and altered sensorium in CKD

A prevalence of 16%–38% has been cited for the spectrum of cognitive dysfunctions in CKD.²⁹ In the early stages of CKD, patients demonstrate poor concentration,

short attention span, emotional disturbance, depression, preoccupation, apathy, and impairment of recent memory. Severe deterioration of renal function can lead to impaired sensorium, delirium, delusions, and hallucinations. In some patients, hallucinations and delusions may lead to agitation and aggressive behavior.

A large number of factors and mechanisms have been implicated in the pathogenesis of cognitive decline and encephalopathy associated with uremia. Kidney failure is associated with accumulation of numerous endogenous and exogenous substances in the blood and body fluids which are toxic to the brain. There is now evidence that blood brain barrier is altered and becomes more permeable in kidney failure allowing influx of noxious agents to the brain. Impairment of the blood-brain barrier in CKD is, in part, mediated by systemic inflammation which is a constant feature of chronic renal failure.^{30–32} In the presence of systemic inflammation, cytokines and chemokines including different interleukins reach the brain tissue and inflict damage to neurons and astrocytes.³³ In fact, pyknosis and apoptosis of hippocampal neurons have been demonstrated in uremic animal models.³⁴

Reduced renal clearance of homocysteine in renal failure often leads to increased blood level homocysteine (>15 $\mu\text{mol/L}$) and its conversion to homocystic acid which via activation of NMDA receptors³⁵ causes neurotoxicity. In addition, homocystic acid can cause endothelial dysfunction and exert a pro-thrombotic effect.³⁶ Further evidence indicates that both albuminuria and decreased GFR singularly and independently correlate with cognitive decline among patients with renal failure.³⁷ Uremia itself may impair the blood-brain barrier and make it more permeable to circulating toxic chemicals and inflammatory substances. In vivo and in vitro experiments have shown that elevated urea at clinically relevant concentrations can destroy the intestinal epithelial tight junction apparatus and allow entry of toxic material into the blood stream.^{38,39} In addition, uremia is invariably associated with oxidative stress. Oxidative stress results in conversion of nitric oxide to toxic peroxynitrite which leads to protein and lipid peroxidation and neuronal damage.^{39,40} In fact, increased neuronal apoptosis has been demonstrated in the hippocampal tissue of rats with renal failure induced by subtotal nephrectomy.³³

Poor clearance of drugs and their increased penetration through blood-brain barrier is another factor which plays a role in neurotoxicity and cognitive decline in CKD. In case of opiates, decreased excretion via cation secretory transport system, increases their plasma level (for instance meperidine) leading to lethargy and impaired cognition.

Response to dialysis and renal transplantation

Adequate dialysis improves the cognitive function of uremic patients with peak improvement noted approximately 24 hours after dialysis.⁴¹ Successful renal transplantation improves all aspects of cognitive function shortly after successful transplantation except for memory which may take up to 1 year to show any notable improvement.⁴²

Dialysis disequilibrium syndrome

Rapid and infrequent hemodialysis treatment results in acute symptoms characterized by headaches, confusion, delirium, and seizures—a condition designated as dialysis disequilibrium syndrome (DDS). DDS usually occurs toward the end of the dialysis session. Neuro-imaging studies (CT, MRI) demonstrate diffuse brain edema which is attributed to the faster removal of urea from extracellular fluid compartment than intracellular compartment. The resulting osmotic disequilibrium leads to acute brain edema due to the rapid influx of water into brain tissue. This phenomenon is, in part, mediated by downregulation of brain urea transporter, upregulation of water transporters-aquaporin (AQ4 and AQP9) and increased production of certain osmolites such as taurine, glutamate, sorbitol, and inositol in the CKD brain tissue.⁴³ Administration of mannitol results in reduction of brain edema and significant improvement of clinical symptoms of DDS.⁴⁴ Introduction of the slower rate and more frequent dialysis has significantly reduced the incidence of DDS.

Dialysis dementia

Dialysis dementia is a progressive and fatal disorder which is related to aluminum toxicity caused by high levels of aluminum in the dialysate and use of aluminum-based phosphate binders.⁴⁵ The affected patients develop a rapidly progressive and often irreversible dementia. Water purification and use of nonaluminum phosphate binders have dramatically reduced prevalence of dialysis dementia.⁴⁶

Epileptic seizures and movement disorders

Severe cognitive decline in kidney disease and uremic encephalopathy,⁴⁷ can be associated with clinical symptoms of cortical excitability such as epileptic seizures, myoclonus, and asterixis.⁴⁸

Epileptic seizures of generalized tonic-clonic type can occur in CKD but are more common in patients with acute renal injury. Among metabolic encephalopathies, uremic encephalopathy more often causes seizures.^{1,2} A variety of factors in CKD can irritate the cerebral cortex and cause seizures. Secondary hyperparathyroidism is a common consequence of advanced kidney disease.⁴⁹ Parathyroid hormone enhances the function of calcium transporters in the brain and the calcium content of the

brain is increased in uremia. Increased intracellular calcium leads to neuronal hyper-excitability. Guanido compounds which are increased in the cerebrospinal fluid of patients with uremia suppress the function of Gabaergic receptors and enhance NMDA receptor function—both of which are capable of inducing cortical excitation.⁵⁰ Changes in GABA, nor-epinephrine, and acetylcholine in the brain of uremic patients also contribute to enhanced depolarization of cortical neurons.⁵¹

Myoclonus is a movement disorder characterized by rapid limb or body jerks usually lasting less than 100 milliseconds. Myoclonus can be of cortical or subcortical in origin. Cortical myoclonus is a fast type of myoclonus with a duration of 50 milliseconds or less. Repetitive cortical myoclonus can lead to generalized tonic-clonic seizures. In some patients with CKD, myoclonus is multifocal and small in amplitude (mini-myoclonus) and hence can be easily overlooked.

Asterixis, sometimes called negative myoclonus, is inability to maintain a fixed position, best seen in the extended hands as a flapping motion.⁵² Asterixis is not specific to renal disease and can be seen in other metabolic disorders specifically hepatic encephalopathy. Asterixis and myoclonus usually disappear after improvement of renal encephalopathy.

Subcortical brain changes and subcortical symptoms in CKD

Two major forms of subcortical pathology have been shown to be associated with uremic encephalopathy. These are white matter changes and posterior reversible encephalopathy.

White matter changes

White matter changes in the brain are seen in advanced age, diabetes, hypertension, ischemia, and anemia.⁵³ Histologically, white matter changes represent axonal degeneration and local areas of brain edema. The MRI of patients with CKD demonstrates significantly higher incidence of extensive white matter changes in the brain—33% among patients with CKD versus 6% among age matched controls.⁵⁴ It has been shown that extensive subcortical white matter changes in the brain correlate with increased risk of cognitive decline and dementia.

Posterior reversible encephalopathy

This entity is a clinical condition characterized by encephalopathy and MRI findings of subcortical (white matter)

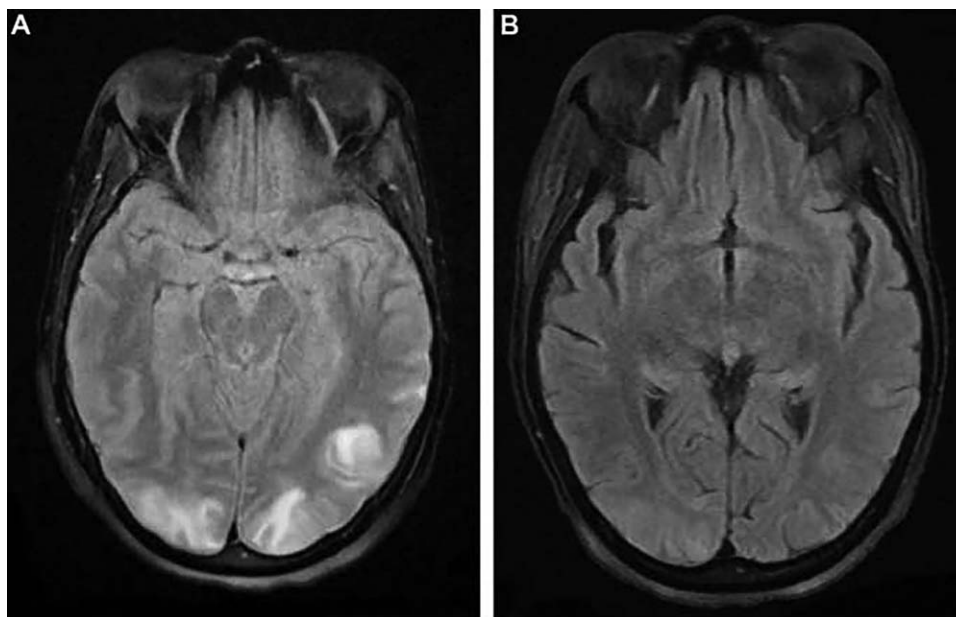


Figure 4 Posterior reversible encephalopathy. (A) High signal changes seen in MRI at parieto- occipital regions associated with encephalopathy. (B) Changes cleared after improvement of the renal failure. Reprinted with permission from Chowdhary et al. *Neuropsychiatr Dis Treat* 2015, DovePress.

edema affecting predominantly the posterior region of the brain.⁵⁵ Severe hypertension is the usual culprit with or without kidney disease. The subcortical white matter changes usually improve or disappear with control of hypertension. Although posterior reversible encephalopathy in patients with kidney failure is usually attributed to hypertensive encephalopathy, it has been reported sometimes in patients with kidney disease in the absence of hypertension, implicating the role of uremia itself in white matter edema.⁵⁶ Improvement in kidney function often results in improvement of encephalopathy and abnormal posterior MRI signals (Figure 4).

Parkinsonism and involuntary movements (chorea, tremor, dystonia)

Recognition of the symptoms specifically related to basal ganglia damage (a subcortical structure) in renal failure is a relatively new observation. These symptoms are usually in form of Parkinsonism, involuntary movements (chorea, tremor, dystonia, subcortical myoclonus) and often present as complication of subcortical strokes.^{57–59} A majority of these patients have diabetic nephropathy although serum glucose may be normal or not as high as that seen in diabetic ketoacidosis which is known to cause dysfunction of basal ganglia and involuntary movements. Hence,

it is currently believed that uremia also plays a role in these complications as an independent factor.

In uremic encephalopathy, magnetic resonance imaging often shows signal abnormalities in the basal ganglia with frequent involvement of putamen presenting as an increase in T1 and a decrease T2 sequences. In one study,⁶⁰ bilateral MRI high signal abnormalities (T1) of dialysis patients correlated with high serum magnesium levels. The basal ganglia related symptoms of Parkinsonism, chorea, dystonia, and tremor along with signal abnormalities in MRI disappear or significantly improve after reversal of kidney failure following renal transplantation. Reversible signal abnormalities in basal ganglia have been attributed to cytotoxic edema and demyelination.^{61,62}

Reticular myoclonus

Reticular myoclonus is a form of subcortical myoclonus with a short duration of 50 milliseconds or less similar to cortical myoclonus. The rapid body jerks are stimulus sensitive and involve proximal as well as distal muscles. Chadwick and French⁶³ believed that much of myoclonic jerks seen in uremia are of reticular reflex type. Infusion of urea into the rat's blood stream has been shown to cause this form of myoclonus which seems to originate from the reticular formation of the brain stem's nucleus gigantocellularis below the midbrain level.⁶⁴

Restless legs syndrome

Patients with restless legs syndrome (RLS) experience unpleasant sensations with urge to move the legs in the evenings or at night which often interfere with initiation of sleep. Restless legs syndrome is often associated with periodic leg movements which disturb sleep and lead to frequent arousals. These movements typically consist of extension and dorsiflexion of the toes, and in more severe cases, flexion of the knee and thighs. Depletion of iron in the CNS plays a major role in pathogenesis of RLS. Iron is a co-factor for tyrosine hydroxylase an enzyme that synthesizes dopamine. Dopamine modulates the function of motor and sensory spinal cord neurons and decreased dopamine levels in CNS contributes to RLS symptoms. Patients with CKD often have iron deficiency and anemia with low ferritin and low serum transferrin saturation.

Trenkwalder et al.⁶⁵ recently reviewed the issue of RLS in major medical diseases from 14 available studies with an observational cross-sectional design. The recorded prevalence of RLS in chronic kidney disease was 68% for U.S. and Western European countries. Factors associated with an increased risk for RLS included caucasian ethnicity, lower serum transferrin saturation, intake of calcium channel blockers, lower parathyroid hormone at baseline, longer duration and frequency of dialysis, number of additional comorbidities, lower education levels, and obstructive sleep apnea.

Treatment of RLS consists of oral or intravenous iron supplementation. Symptoms respond to dopaminergic drugs; pramipexole, ropinirole, and rotigotine (skin patch). Gabapentin and pregabalin are also effective.

Stroke and chronic kidney disease

Occlusive or hemorrhagic cerebrovascular disease is the cause of many of the above cited cortical and subcortical neurological symptoms in CKD. In 2006, the United States renal data system reports noted the annual incidence of stroke in chronic renal disease as 10% compared to 2.5% in the general population.⁶⁶ The risk of stroke for dialysis patients in general has been reported to be 5 times higher than that of normal population and it is particularly higher in hemodialysis patients (4–10 times).⁶⁷ Among dialysis patients, those with diabetes and nephrosclerosis are more prone to develop stroke earlier. Other risk factors include black or hispanic ethnicity and older age as well as presence of known risk factors such as hypertension and heart disease. Intracerebral hemorrhage is more common in hemodialysis patients, due to changes in coagulation system and recurrent anticoagulation with heparin

administration. In fact, neuro-imaging data (CT and MRI) demonstrate microbleeds in the brain paranchyma of 26%–61% of hemodialysis patients.⁶⁸ Chronic renal disease itself can facilitate development of stroke via presence of several factors: oxidative stress, systemic inflammation, coagulation abnormalities, dyslipidemia, and hyperhomocysteinemia to mention a few. In addition, CKD is associated with higher incidence of medical disorders which are potential risks for stroke. For instance, the incidence of atrial fibrillation in patients with chronic kidney disease has been reported as 7%–27% which is considerably higher than that in the general population.⁶⁹ Chronic kidney disease can also worsen the course of an ongoing stroke by inflicting further damage to the endothelial tissue via elevated cytokines and other inflammatory mediators in the circulation. In fact, the intima and media of carotid arteries are significantly thicker in patients with CKD than that of age-matched general population.⁷⁰

A glomerular filtration rate (GFR) of below 60 ml/min and presence of albuminuria are independent risk factors for stroke in patients with CKD.⁷¹ The data from British Regional Heart Study demonstrate that the risk of stroke is increased significantly in CKD patients with a serum creatinine level exceeding 1.3 dl.⁷² In a recent study of 3932 patients with CKD of whom 143 had stroke, after correction for confounding factors, proteinuria levels exceeding 0.5 g/dl and albuminuria exceeding 30 mg/dl showed significantly higher correlations with the incidence of stroke than GFR.⁷³ Another recent review identified 30,392 cases of strokes in 83 studies derived from 20 randomized clinical trials (68,516 participants). The risk of stroke increased by 7% for every 10 ml/min/1.73 m² decrease in GFR. A 25 mg/mmol increase in albumin/creatinine ratio correlated with a 10% increased risk of stroke. The effect of albuminuria was independent of GFR.⁷⁴ The association of proteinuria with increased risk of stroke is most likely due to its well-known effect on blood coagulation system.^{75–77}

Prevention and management of stroke in patients with CKD

In a recent review, Tonelli et al.⁷⁸ discussed challenges in prevention and management of stroke in chronic kidney disease. The challenge is in part related to scant clinical trials and paucity of controlled data.

Prevention and management of known risk factors such as obesity, hypertension, and diabetes is essential in reducing the risk of stroke. Treatment with aspirin is advocated by most in the CKD stages 1 and 2, but remains controversial in the higher stages. Strategies aimed at improving GFR and reducing albuminuria are effective in reducing

the risk of stroke in this population. Measurement of carbamylated albumin may prove to be a better prognostic indicator of morbidity and mortality than proteinuria.⁷⁹ The utility of statins for stroke prevention in CKD remains unproven but a recent meta-analysis of 6 clinical trials conducted between 2012 and 2013 suggests efficacy in prevention of cardiovascular complications in patients with CKD.⁸⁰ Some studies suggest that daily hemodialysis instead of 3 times per week lowers the blood pressure and, hence, indirectly lowers the risk of stroke.⁸¹

Management of stroke in patients with CKD is complicated due to increased risk and side effects of the therapeutic interventions. Jung et al.⁸² reviewed the data on the use of tissue plasminogen activator in 7168 patients with acute stroke, 28% of whom had CKD. Patients with CKD had an increased risk of intracerebral hemorrhage and were more likely to have a poorer outcome at 3 months. Dad and Weiner⁸³ in a recent manuscript, recommended that for individuals with CKD who do not require dialysis, the prevention and management of stroke can be similar to the approach in the general population. For individuals with end-stage renal disease, far less is known regarding strategies to prevent stroke. The benefit of stroke prophylaxis using warfarin in dialysis patients with atrial fibrillation is uncertain. End-stage renal disease patients can be managed aggressively in the setting of acute stroke. Outcomes after stroke at all stages of CKD are poorer compared to general population, and improving these outcomes should be the subject of future investigations.

CONCLUSION

Chronic kidney disease results in a variety of neurological disorders that involve both peripheral and CNS. The CKD-associated neurological disorders contribute to physical and mental disabilities and impaired quality of life in this vulnerable population. While considerable progress has been made in the understanding of the features of the CKD-associated neurological disorders, many unanswered questions remain which require future investigations to define the mechanisms of and effective treatments for these disabling complications.

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REFERENCES

- 1 Raskin NH, Fishman RA. Neurologic disorders in renal failure (first of two parts). *N Engl J Med.* 1976; **294**: 143–148.
- 2 Raskin NH, Fishman RA. Neurologic disorders in renal failure (second of two parts). *N Engl J Med.* 1976; **294**: 204–210.
- 3 Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA.* 2007; **298**:2038–2047.
- 4 Asbury AK. Uremic polyneuropathy. In: Dyck, PJ, Thomas, PK, eds. *Peripheral Neuropathy*, 3rd edn. Philadelphia: WB Saunders. 1993; 1251–1257.
- 5 Vaziri D, Pratt H, Saiki JK, Starr A. Evaluation of somatosensory pathway by short latency evoked potentials in patients with end-stage renal disease maintained on hemodialysis. *Int J Artif Organs.* 1981; **4**: 17–22.
- 6 Kiernan M, Walters R, Andersen K, et al. Nerve excitability changes in chronic renal failure indicate membrane depolarization due to hyperkalemia. *Brain.* 2002; **125**:1366–1375.
- 7 Krishnan AV, Phoon RKS, Pussell BA, et al. Altered motor nerve excitability in end-stage kidney disease. *Brain.* 2005; **28**:2164–2174.
- 8 Baumgaertel MW, Kraemer M, Berlit P. Neurologic complications of acute and chronic renal disease. *Handb Clin Neurol.* 2014; **119**:383–393.
- 9 Dang DH, Carter AL, Olin JL, Velasco JC. Baclofen-induced encephalopathy in an older patient with stage 2 chronic kidney disease. *J Am Pharm Assoc (2003).* 2015; **55**:117–118.
- 10 Kaufman KR, Parikh A, Chan L, Bridgeman M, Shah M. Myoclonus in renal failure: Two cases of gabapentin toxicity. *Epilepsy Behav Case Rep.* 2013; **2**:8–10.
- 11 Albertazzi A, Cappelli P, Di Marco T, Maccarone M, Di Paolo B. The natural history of uremic neuropathy. *Contrib Nephrol.* 1988; **65**:130–137.
- 12 Ho DT, Rodig NM, Kim HB, et al. Rapid reversal of uremic neuropathy following renal transplantation in an adolescent. *Pediatric Transplant.* 2012; **16**:E296–E300.
- 13 Antonelli AR, Bonfioli F, Garrubba V, et al. Audiological findings in elderly patients with chronic renal failure. *Acta Otolaryngol Suppl.* 1990; **476**:54–68.
- 14 Shvili Y, Gafter U, Zohar Y, Talmi YP, Levi J. Brainstem auditory evoked responses in rats with experimental chronic renal failure. *Clin Sci.* 1989; **76**:415–417.
- 15 Rossini PM, Di Stefano E, Febbo A, Di Paolo B, Basciani M. Brain-stem auditory evoked responses (BAERs) in patients with chronic renal failure. *Electroencephalogr Clin Neurophysiol.* 1984; **57**:507–514.
- 16 Komsuoglu SS, Mehta R, Jones LA, Harding GF. Brainstem auditory evoked potentials in chronic renal failure and maintenance hemodialysis. BAEP in dialysis: I and III-V prolonged and reversed by dialysis. *Neurology.* 1985; **35**:419–423.
- 17 Mirahmadi MK, Vaziri ND. Hearing loss in end-stage renal disease effect of dialysis. *J Dial.* 1980; **4**:159–165.

- 18 Griep MI, Van der Niepen P, Sennesael JJ, Mets TF, Massart DL, Verbeelen DL. Odour perception in chronic renal disease. *Nephrol Dial Transplant*. 1997; **12**:2093–2098.
- 19 Frasnelli JA, Temmel AF, Quint C, Oberbauer R, Hummel T. Olfactory function in chronic renal failure. *Am J Rhinol*. 200; **16**:275–279.
- 20 Saini JS, Jain IS, Dhar S, Mohan K. Uremic optic neuropathy. *J Clin Neuroophthalmol*. 1989; **9**: 131–133.
- 21 Hamel B, Bourne JR, Ward JW, Teschan PE. Visually evoked cortical potentials in renal failure: Transient potentials. *Electroencephalogr Clin Neurophysiol*. 1978; **44**:606–616.
- 22 Cohen SN, Syndulko K, Rever B, Kraut J, Coburn J, Tourtellotte WW. Visual evoked potentials and long latency event-related potentials in chronic renal failure. *Neurology*. 1983; **33**:1219–1222.
- 23 Brown JJ, Sufit RL, Sollinger HW. Visual evoked potential changes following renal transplantation. Visual evoked potential changes following renal transplantation. *Electroencephalogr Clin Neurophysiol*. 1987; **66**:101–107.
- 24 Campistol JM. Uremic myopathy. *Kidney Int*. 2002; **62**: 1901–1913.
- 25 Qureshi AR, Alvestrand A, Danielsson A, et al. Factors predicting malnutrition in hemodialysis patients: a cross-sectional study. *Kidney Int*. 1998; **53**:773–782.
- 26 Yazdi PG, Moradi H, Yang JY, Wang PH, Vaziri ND. Skeletal muscle mitochondrial depletion and dysfunction in chronic kidney disease. *Int J Clin Exp Med*. 2013; **6**: 532–539.
- 27 Mak RH, DeFronzo RA. Glucose and insulin metabolism in uremia. *Nephron*. 1992; **61**:377–382.
- 28 Vaziri ND. Anemia and anemia correction: Surrogate markers or causes of morbidity in chronic kidney disease? *Nat Clin Pract Nephrol*. 2008; **4**:436–445.
- 29 Kurella M, Mapes DL, Port FK, Chertow GM. Correlates and outcomes of dementia among dialysis patients: The dialysis outcomes and practice patterns study. *Nephrol Dial Transplant*. 2006; **21**:43–48.
- 30 Yoon JW, Pahl MV, Vaziri ND. Spontaneous leukocyte activation and oxygen-free radical generation in end-stage renal disease. *Kidney Int*. 2007; **71**: 167–172.
- 31 Ruiz S, Pergola PE, Zager RA, Vaziri ND. Targeting Nrf2 activation to ameliorate oxidative stress and inflammation in Chronic Kidney Disease. *Kidney Int*. 2013; **83**:1029–1041.
- 32 Vaziri ND, Yuan J, Rahimi A, Ni Z, Said H, Subramanian VS. Disintegration of colonic epithelial tight junction in uremia: A likely cause of CKD-associated inflammation. *Nephrol Dial Transplant*. 2012; **27**:2686–2693.
- 33 Sonnevile R, Verdonk F, Rauturier C, et al. Understanding brain dysfunction in sepsis. *Ann Intensive Care*. 2013; **3**:3–15.
- 34 Fujisaki K, Tsuruya K, Yamato M, et al. Cerebral oxidative stress induces spatial working memory dysfunction in uremic mice: Neuroprotective effect of tempol. *Nephrol Dial Transplant*. 2014; **29**:529–538.
- 35 Lipton SA, Kim WK, Choi YB, et al. Neurotoxicity with dual actions of homocysteine at the N-methyl-D spartate receptor. *Proc Natl. Acad Sci USA*. 1997; **94**: 5923–5928.
- 36 Fassbender K, Mielke O, Bertsch T, Nafe B, Fröschen S, Hennerici M. Homocysteine in cerebral macroangiography and microangiopathy. *Lancet*. 1999; **353**: 1586–1587.
- 37 Umemura T, Kawamura T, Umegaki H, et al. Association of chronic kidney disease and cerebral small vessel disease with cognitive impairment in elderly patients with type 2 diabetes. *Dement Geriatr Cogn Disord Extra*. 2013; **3**:212–222.
- 38 Vaziri ND, Zhao YY, Pahl MV. The impact of CKD on the intestinal microbiome and epithelial barrier structure and function. *Nephrol Dial Transplant*. 2016; **31**:737–746.
- 39 Deng G, Vaziri ND, Jabbari B, Ni Z, Yan XX. Increased tyrosine nitration of the brain in chronic renal insufficiency: Reversal by antioxidant therapy and angiotensin converting enzyme inhibition. *J Am Nephrol*. 2001; **12**:1892–1899.
- 40 Bernstein HG, Bogerts B, Keilhoff G. The many faces of nitric oxide in schizophrenia. A review. *Schizophr Res*. 2005; **78**:69–86.
- 41 Lewis EG, O'Neill WM, Dustman RE, Beck EC. Temporal effects of hemodialysis on measures of neural efficiency. *Kidney Int*. 1980; **17**:357–363.
- 42 Radic J, Ljutić D, Radić M, Kovačić V, Dodig-Ćurković K, Šain M. Kidney transplantation improves cognitive and psychomotor functions in adult haemodialysis patients. *Am. J. Nephrol*. 2011; **34**:399–406.
- 43 Trinh-Trang-Tan MM, Cartron JP, Bankir L. Molecular basis for the dialysis disequilibrium syndrome: altered aquaporin and urea transporter expression in the brain. *Nephrol Dial Transplant*. 2005; **20**: 984–1988.
- 44 Rodrigo F, Shideman J, Mchugh R, Buselmeier T, Kjellstrand C. Osmolality changes during haemodialysis. Natural history, clinical correlations, and influence of dialysate glucose and intravenous mannitol. *Ann Intern Med*. 1977; **86**:554–561.
- 45 Watanabe K, Watanabe T, Nakayama M. Cerebro-renal interactions: Impact of uremic toxins on cognitive function. *Neurotoxicology*. 2014; **44**:184–193.
- 46 Chertow GM. Correlates and outcomes of dementia among dialysis patients: The dialysis outcomes and practice patterns study. *Nephrol Dial Transplant*. 2006; **21**:2543–2548.

- 47 Seifter JL, Samuels MA. Uremic encephalopathy and other brain disorders associated with renal failure. *Semin Neurol*. 2011; **31**:139–143.
- 48 Lacerda G, Krummel T, Hirsch E. Neurologic presentations of renal diseases. *Neurol Clin*. 2010; **28**:45–59.
- 49 Fraser CL, Arieff AI. Nervous system complications in uremia. *Ann Intern Med*. 1988; **109**:143–153.
- 50 De Deyn PP, D'hooge R, Van Bogaert PP, Mareskau B. Endogenous guanidine compounds as uremic neurotoxins. *Kidney Int*. 2001; **59**:S77–S83.
- 51 Smogorzewski MJ. Central nervous dysfunction in uraemia. *Am J Kidney Dis*. 2001; **38**:s122–s128.
- 52 Toro C, Hallett M, Rothwell JC, Asselman PT, Marsden CD. Physiology of negative myoclonus. *Adv Neurol*. 1995; **67**:211–217.
- 53 DeBette S, Beiser A, DeCarli C, et al. Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality: The Framingham Offspring Study. *Stroke*. 2010; **41**:600–606.
- 54 Martinez-Vea A, Salvadó E, Bardají A, et al. Silent cerebral white matter lesions and their relationship with vascular risk factors in middle-aged predialysis patients with CKD. *Am J Kidney Dis*. 2006; **47**:241–250.
- 55 Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukocephalopathy syndrome. *N Engl J Med*. 1996; **334**:494–500.
- 56 Iwafuchi Y, Okamoto K, Oyama Y, Narita I. Posterior reversible encephalopathy syndrome in a patient with severe uremia without hypertension. *Intern Med*. 2016; **55**:63–68.
- 57 Wang HC, Cheng SJ. The syndrome of acute bilateral basal ganglia lesions in diabetic uremic patients. *J Neurol*. 2003; **250**:948–955.
- 58 Lin HL, Lin HC, Chen YH. Increased risks of parkinsonism in the 3 years after chronic renal failure. *Int J Clin Pract*. 2012; **66**:499–503.
- 59 Wang H-C, Hsu JL, Shen Y Y. Acute bilateral basal ganglia lesions in patients with diabetic uremia: An FDG-PET study. *Clin Nucl Med*. 2004; **29**:475–478.
- 60 da Silva CJ, da Rocha AJ, Jeronymo S, et al. A preliminary study revealing a new association in patients undergoing maintenance hemodialysis: Manganism symptoms and T1 hyperintense changes in the basal ganglia. *AJNR Am J Neuroradiol*. 2007; **28**:1474–1479.
- 61 Lin JJ. Generalized chorea in the syndrome of acute bilateral basal ganglia lesions in patients with diabetic uremia. *J Clin Neurosci*. 2011; **18**:1266–1268.
- 62 Tajima Y, Mito Y, Yanai M, Fukazawa Y. Unusual basal ganglia lesions in a diabetic uraemic patient proven to be demyelination: First pathological observation. *BMJ Case Rep*. 2012; 2012: pii: bcr2012006522.
- 63 Chadwick D, French AT. Uraemic myoclonus: An example of reticular reflex myoclonus? *J Neurol Neurosurg Psychiatr*. 1979; **42**:52–55.
- 64 Zuckerman EG, Glaser GH. Urea induced myoclonic seizures. *Arch Neurol*. 1972; **27**:5–27.
- 65 Trenkwalder C, Allen R, Högl B, Paulus W, Winkelmann J. Restless legs syndrome associated with major diseases: A systematic review and new concept. *Neurology*. 2016; **86**:1336–1343.
- 66 United States Renal Data System 2006 Annual Report. Morbidity & mortality. Neuroepidemiology: Incident & prevalent stroke [online], 2006. Available from: http://www.usrds.org/2006/pdf/06_morb_morte_06.pdf
- 67 Nakatani T, Naganuma T, Uchida J, et al. Silent cerebral infarction in hemodialysis patients. *Am J Nephrol*. 2003; **23**:86–90.
- 68 Kobayashi M, Kobayashi M, Hirawa N, et al. Relationship between silent brain infarction and chronic kidney disease. *Nephrol Dial Transplant*. 2009; **24**:201–207.
- 69 Aronow WS. Acute and chronic management of atrial fibrillation in patients with late-stage CKD. *Am J Kidney Dis*. 2009; **53**:701–710.
- 70 Desbien AM, Chonchol M, Gnahn H, Sander D. Kidney function and progression of carotid intima-media thickness in a community study. *Am J Kidney Dis*. 2008; **51**:584–593.
- 71 Toyoda K, Ninomiya T. Stroke and cerebrovascular diseases in patients with chronic kidney disease. *Lancet Neurol*. 2014; **13**:823–833.
- 72 Wanamethee SG, Shaper AG, Perry IJ. Serum creatinine concentration and risk of cardiovascular disease: A possible marker for increased risk of stroke. *Stroke*. 1997; **28**:557–563.
- 73 Sandsmark DK, Messé SR, Zhang X, et al. CRIC study investigators. Proteinuria, but not eGFR, predicts stroke risk in chronic kidney disease: Chronic renal insufficiency cohort study. *Stroke*. 2015; **46**:2075–2080.
- 74 Masson P, Webster AC, Hong M, Turner R, Lindley RI, Craig JC. Chronic kidney disease and the risk of stroke: A systematic review and meta-analysis. *Nephrol Dial Transplant*. 2015; **30**:1162–1169.
- 75 Vaziri ND. Nephrotic syndrome and coagulation and fibrinolytic abnormalities. *Am J Nephrol*. 1983; **3**:1–6.
- 76 Vaziri ND, Branson H, Ness R. Changes of coagulation factors IX, VIII, VII, X, and V in nephrotic syndrome. *Am J Med Sci*. 1980; **280**:167–171.
- 77 Vaziri ND, Paule P, Toohey J, et al. Acquired deficiency and urinary excretion of antithrombin III in nephrotic syndrome. *Arch Intern Med*. 1984; **144**:1802–1803.
- 78 Tonelli M, Karumanchi SA, Thadhani R. Epidemiology and mechanisms of uremia-related cardiovascular disease. *Circulation*. 2016; **133**:518–536.

- 79 Drechsler C, Kalim S, Wenger JB, et al. Protein carbamylation is associated with heart failure and mortality in diabetic patients with end-stage renal disease. *Kidney Int.* 2015; **87**:1201–1208.
- 80 Major RW, Cheung CK, Gray LJ, Brunskill NJ. Statins and cardiovascular primary prevention in CKD: A meta-analysis. *Clin J Am Soc Nephrol.* 2015; **10**:732–739.
- 81 Kotanko P, Garg AX, Depner T, et al. Effects of frequent hemodialysis on blood pressure: Results from the randomized frequent hemodialysis network trials. *Hemodial Int.* 2015; **19**:386–401.
- 82 Jung JM, Kim HJ, Ahn H, et al. Chronic kidney disease and intravenous thrombolysis in acute stroke: A systematic review and meta-analysis. *J Neurol Sci.* 2015; **358**:345–350.
- 83 Dad T, Weiner DE. Stroke and chronic kidney disease: Epidemiology, pathogenesis, and management across kidney disease stages. *Semin Nephrol.* 2015; **35**: 311–322.