Section A-Research paper

Brief Overview about Chronic Kidney Disease and related Neurodegenerative Disorders

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Abstract

Background: The definition and classification of Chronic kidney disease (CKD) have evolved over time, but current international guidelines define CKD as decreased kidney function shown by Glomerular filtration rate (GFR) of less than 60 mL/min per 1.73 m2, or markers of kidney damage, or both, of at least 3 months duration, regardless of underlying cause. A prolonged decline in renal function and structural damage to the kidneys are prerequisites for the diagnosis of CKD. CKD is caused by a variety of diverse disease processes that, over the course of months or years, permanently impair the kidney's structure and function. Peripheral neuropathy caused by CKD is triggered by a number of factors. Significant axonal depolarization has been observed in CKD in the early stages of neuropathy. The acoustic and olfactory nerves are particularly vulnerable to the harmful consequences of uremia. In approximately 40% of those with CKD who participated in a brain stem auditory evoked potential (BAEP) investigation, the I-III interpeak intervals were prolonged, indicating the presence of auditory neuropathy. Following the start of hemodialysis, BAEP abnormalities improved or normalised in some individuals. Peritoneal dialysis does not help individuals with chronic kidney disease's hearing loss, according to prior studies. Patients with uremia can develop a classic myopathy, which is characterized by proximal muscular weakness, muscle atrophy, and typical electromyographic characteristics of myopathy

Keywords: Neurodegenerative Diseases, Chronic Kidney Disease

Introduction

The definition and classification of Chronic kidney disease (CKD) have evolved over time, but current international guidelines define CKD as decreased kidney function shown by Glomerular filtration rate (GFR) of less than 60 mL/min per 1.73 m^2, or markers of kidney damage, or both, of at least 3 months duration, regardless of underlying cause**.** GFR, which measures the total volume of fluid that is filtered through all of the working nephrons in a given amount of time, is the best indicator currently known of kidney function as a whole **(1).**

When GFR is less than 15 mL/min per 73m^2, a person has reached end stage kidney disease (ESKD), at which point kidney function is no longer able to sustain life over the long term. Options for patients with ESKD are kidney replacement therapy (in the form of dialysis or kidney transplantation), or conservative care (also called palliation or non-dialytic care) **(2).**

A prolonged decline in renal function and structural damage to the kidneys are prerequisites for the diagnosis of CKD. CKD is caused by a variety of diverse disease processes that, over the course of months or years, permanently impair the kidney's structure and function **(3).**

Epidemiology of CKD

The incidence and prevalence of CKD vary globally according to ethnicity and social class, progression also differs between nations. The risk of developing progressive CKD is 60% higher in individuals in the lowest socioeconomic quartile than in those in the highest quartile **(4).**

Pathophysiology

The final common pathological manifestation of many chronic kidney diseases is renal fibrosis. Glomerulosclerosis, tubular atrophy, and interstitial fibrosis are characteristics of renal fibrosis, which is the ineffective wound-healing of kidney tissue after chronic, prolonged injury. Glomerulosclerosis is brought on by endothelial damage and malfunction, proliferation of smooth muscle cells and mesangial cells, and degeneration of podocytes, which normally line the glomerular basement membrane. Smoking, dyslipidemia, and hypertension are all risk factors for progressive glomerulosclerosis **(5).**

Glomerular microinflammation is initiated following activation of endothelial cells in response to hypertension, with inflammatory cells (including macrophages and foam cells) activating mesangial cells to proliferate **(6).**

Transforming growth factor ß1 and other growth factors (including platelet-derived growth factor, fibroblast growth factor, tumour necrosis factor, and interferon gamma) stimulate mesangial cells to regress to mesangioblasts (immature mesangial cells). These mesangioblasts are capable of producing an excessive extracellular matrix, leading to mesangial expansion an early sign of glomeruloscelrosis ,stretching of podocytes leaves areas of the glomerular basement membrane exposed to Bowman's capsule with which it forms adhesions, thus contributing to glomerulosclerosis.Tubular atrophy, interstitial fibrosis, and scarring are closely associated with GFR and proteinuria. Tubular epithelial cells are stimulated to synthesize inflammatory products including reactive oxygen species and chemokines by various abnormally-filtered urinary proteins, including complement, cytokines, and albumin **(2).**

These agents attract inflammatory cells into the renal interstitium and initiate interactions with interstitial myofibroblasts. As fibrosis evolves, injured tubular epithelia lose their regenerative capacity and undergo apoptosis leading to tubular atrophy and creating nonfunctional glomeruli. Histologically, measures of tubular cell area are closely associated with GFR. Kidneys are metabolically highly active with a high oxygen requirement. Early in CKD injury, interstitial capillaries become increasingly permeable (the kidney capillary leak syndrome) meaning that many plasma proteins that normally never reach the renal interstitium are able to do so and trigger an inflammatory response **(7).**

A progressive decline in the surface area of interstitial capillaries leads to hypoxia within the kidney and affects the function of cells usually involved in the degradation of collagen which is synthesised and degraded by matrix metalloproteinases, serine proteases and lysosomal enzymes) in healthy kidneys**(2).** Collagens (particularly fibrillar collagen I and II), basement membrane proteins, proteoglycans, and glycoproteins become deposited in the chronically damaged kidney; the area of fibrotic interstitium affected is closely associated with both renal function and long-term renal prognosis **(2).**

Clinical presentation, signs, symptoms and complications

Many patients with CKD are asymptomatic and don't show symptoms until they are sick with severe CKD or after chance discoveries from screening tests, such as during a routine physical or checkup.

However, depending on the underlying cause of CKD, some individuals have symptoms as a direct result of their deteriorated kidney health. Uraemic retention solutes are a group of compounds that build up in the body as chronic kidney disease (CKD) worsens and kidney function declines; those of these molecules that have negative biological consequences are referred to as uraemic toxins. **(8).**

Uraemic retention products affect almost all of the body's organs and systems, but they don't always accumulate predictably, and kidney function tests may not be able to distinguish between their concentrations and renal function tests. Numerous studies are being conducted with the goal of controlling or improving uraemic toxins in order to lessen uraemic symptoms and ameliorate CKD consequences or decrease the progression of CKD **(9).**

CKD *effect* on the neurological functions:

*1.*Peripheral Neurologic Complications of CKD

Peripheral neuropathy of the limbs has been reported in 50%–60% of patients with end stage renal disease. Motor and sensory axons are both affected by CKD, which is progressive. Patients' everyday activities, sleep, and sometimes-painful sensations, which largely affect their legs, are affected; in more severe cases, patients' quality of life is significantly impacted by their legs' weakness and their unsteadiness **(10).**

Peripheral neuropathy caused by CKD is triggered by a number of factors. Significant axonal depolarization has been observed in CKD in the early stages of neuropathy **(11).** This is because intracellular calcium accumulation related to hyperkalemia in CKD and reversal of the K^{+}/Ca^{+2} pump can induce axonal damage. 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. Furthermore, many drugs which are used for management of CKD are capable of causing peripheral neuropathy **(12).**

2.Cranial neuropathy

The acoustic and olfactory nerves are particularly vulnerable to the harmful consequences of uremia. In approximately 40% of those with CKD who participated in a brain stem auditory evoked potential (BAEP) investigation, the I-III interpeak intervals were prolonged, indicating the presence of auditory neuropathy. Following the start of hemodialysis, BAEP abnormalities improved or normalised in some individuals. Peritoneal dialysis does not help individuals with chronic kidney disease's hearing loss, according to prior studies. **(10).**

The majority of CKD patients do not have substantial visual problems, however uncommon, treatable uremic optic neuropathy may occur in this population. Also, it was reported that, both dialysis-treated and untreated uremic patients have prolonged main P100 of the visual evoked response (VEP). with the return of normal VEP abnormalities after kidney transplantation **(13).**

3. Uremic myopathy

Patients with uremia can develop a classic myopathy, which is characterized by proximal muscular weakness, muscle atrophy, and typical electromyographic characteristics of myopathy **(14)** .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. Several mechanisms have been proposed to

explain the development of uremic myopathy. Renal transplantation is one option for treating uremic myopathy, along with proper renal replacement therapy, better nutrition, carnitine supplementation, secondary hyperparathyroidism management and prevention, synthetic erythropoietin use to treat anaemia, and prevention of secondary hyperparathyroidism. The latter frequently alleviates the myopathy but does not completely recover muscular function **(15).**

4. Disorders of the Central Nervous System in CKD

Cortical symptoms in CKD

Cognitive impairment, delirium, encephalopathy, dementia, focal stroke-related symptoms (paralysis, spasticity), as well as cortically originated abnormal movements such cortical myoclonus, asterixis, and epileptic seizures, are all characteristics of cortical disorder in CKD **(10).**

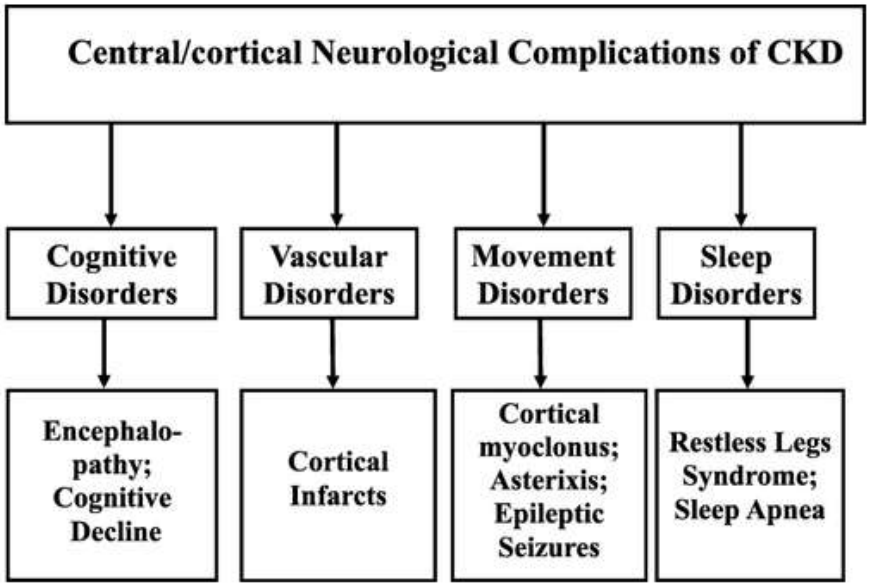

Fig. 1: Central/cortical complications of CKD (10).

Impaired cognition and altered sensorium in CKD

The prevalence of the full range of cognitive dysfunctions in CKD has been estimated to be between 16% and 38%. Patients with CKD exhibit poor concentration, a short attention span, emotional disturbance, depression, obsession, apathy, and impairment of recent memory in the early stages of the disease. Hallucinations, psychosis, delusions, and decreased sensorium can result from severe renal dysfunction. Agitation and aggressive behaviour may result from hallucinations and delusions in some patients **(16).**

The pathophysiology of uremia-related encephalopathy and cognitive impairment has been linked to a wide range of variables and mechanisms. Kidney failure is associated with accumulation of numerous endogenous and exogenous substances in the blood and body fluids which are toxic to the brain. Impairment of the blood-brain barrier in CKD is, in part which make it more permeable to circulating toxins and inflammatory cytokines, mediated by systemic inflammation which is a constant feature of chronic renal failure **(17).** When there is systemic inflammation, cytokines and

chemokines, including various interleukins, enter the brain tissue and harm astrocytes and neurons. In fact, apoptosis of hippocampal neurons have been demonstrated in uremic animal models **(18).**

Reduced renal clearance of homocysteine in renal failure often leads to increased blood level homocysteine (>15 umol/L) and its conversion to homocysteic acid which via activation of N-methyl-D-aspartate (NMDA) receptors causes neurotoxicity. In addition, homocysteic acid can cause endothelial dysfunction and exert a pro-thrombotic effect. Further evidence indicates that both albuminuria and decreased GFR singularly and independently correlate with cognitive decline among patients with renal failure. Oxidative stress results in conversion of nitric oxide to toxic peroxynitrite which leads to protein and lipid peroxidation and neuronal damage. In fact, increased neuronal apoptosis has been demonstrated in the hippocampal tissue of rats with renal failure induced by subtotal nephrectomy **(19).**

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