End-Stage Renal Disease and Neurological Connection

| Authors: | *Raj Kamal Choudhary,¹ Amrendra Kumar Singh,¹ Ravi Raman,² Anjum Perwaz¹

1. Jawaharlal Nehru Medical College and Hospital, Bhagalpur, India
2. Patna Medical College and Hospital, India
*Correspondence to akschinku@gmail.com |

Abstract

Due to the incapacitating nature of end-stage renal disease, people on dialysis frequently acquire undetected psychopathological disorders. This may affect the effectiveness of treatment for a chronic disease. Dialysis is a therapy for kidney failure, but not a cure. As a result of the treatment plan and other restrictions, the patient is forced to make several significant modifications to their daily routines and activities, which in turn has an impact on their ability to socialise and mentally operate. There is a high rate of morbidity and mortality in individuals with renal failure due to neurological complications. Dialysis may not be effective in treating many of the neurological effects of uraemia, such as uraemic encephalopathy, atherosclerosis, neuropathy, and myopathy, despite ongoing improvements in therapy. Brain networks are destroyed in patients on haemodialysis with end-stage renal disease.

Key Points

1. Patients with end-stage renal disease accumulate blood urea and experience nitrogen and electrolyte imbalances due to decreased renal excretion, leading to neurological complications.

2. The Indian healthcare sector has inadequate dialysis facilities, which reduces the frequency of dialysis. This further aggravates neurological complications.

3. Uncontrolled diabetes and uncontrolled hypertension are significant contributors to renal disease. Hence, early and aggressive treatment of hypertension and diabetes can lead to improved patient outcomes for end-stage renal disease.

INTRODUCTION

The complete loss of kidney function characterises the last stage of chronic kidney disease (CKD), known as end-stage renal disease (ESRD). Patients with ESRD often struggle with cognitive impairment. Disabilities in many areas of cognition, such as attention, memory, and planning, may lead to longer treatment times, higher healthcare costs, more frequent hospitalisations, and longer overall hospital stays. Understanding the neural processes at play in ESRD may become possible with increased awareness of the cognitive impairments that accompany the disease, and this in turn may pave the way for preventative measures that might lessen the severity of the condition. ESRD is a devastating health problem with a dismal outlook that affects people all over the world. A recent study found that the incidence of ESRD requiring dialysis treatment was greatest among the Taiwanese population.[1] In the study, people with ESRD had cerebral signs in addition to systemic issues.

Imaging is a vital tool for detecting structural and functional brain disorders in patients with ESRD. Brain volume loss, deep white matter volume loss, a high prevalence of subcortical white matter lesions, and an elevated stroke incidence have all been documented in patients with ESRD in studies of conventional MRI and CT scans with visual assessment and manual measurements of structures of interests.[2,3] Patients with CKD (Stage 4–5) without clinical sign of uremic encephalopathy exhibit MRI spectroscopy-observed metabolic abnormalities in the parieto-occipital white matter, occipital grey matter, basal ganglia, and pons (magnetic resonance spectroscopy). Studies utilising positron emission tomography have shown impaired oxygen and glucose metabolism in the brains of individuals with ESRD, with the effects being most severe in the bilateral prefrontal cortices. Traditional MRI and CT, which rely on subjective visual evaluation and manual measurements of structures of interest, are insensitive to the early and tiny lesions, whereas single-voxel magnetic resonance spectroscopy has a limited spatial resolution and exposes the patient to radiation.[3]

Using resting-state functional MRI (rs-fMRI), subjects may record their own brain's normal fluctuations in activity while at rest in the scanner. Low-frequency (0.01–0.80 Hz) fluctuations in the blood-oxygen-level-dependent signals are connected with spontaneous brain activity and may have physiological implications during the resting state. Recent studies using rs-fMRI and the regional homogeneity analysis method have demonstrated that patients with ESRD had reduced regional homogeneity in various areas of the bilateral frontal, parietal, and temporal lobes.[4] Further, they found a decline in default-mode network (DMN) regional homogeneity,[5] which suggests that frontal and parietal lobes may be trait-related in patients with ESRD with mild nephroencephalopathy. MRIs that provide regional grey matter volume at the voxel scale may be evaluated using a method called voxel-based morphometry, which is both spatially specific and objective. This technique has shown positive results in the treatment of individuals with a variety of conditions, including healthy ageing, schizophrenia, dementia, mild cognitive impairment, addiction, and hepatic encephalopathy. Functional integrity alterations in patients with ESRD may be connected to these morphometric abnormalities, which include significant cerebral atrophy, most notably bilaterally in the caudate nuclei, and diffusely decreased grey matter volume, with higher decreases in the presence of encephalopathy. However, there has been no investigation into how this damaged grey matter could affect function. When voxel-based morphometry is used in tandem with rs-fMRI, scientists may examine both structural and functional brain problems simultaneously. This strategy may prove to be rather effective in learning more about the neurobiological mechanisms at play in patients with ESRD.[6]

AIMS AND OBJECTIVE

This study aims to find out what different types of neurological complications,

fatigue, oxidative stress, cardiovascular complications, infections, neoplasm, and hypertension are seen in patients with ESRD admitted at the authors' institute to facilitate treatment that is more beneficial.

FACTORS CONTRIBUTING TO FATIGUE IN END-STAGE RENAL DISEASE

Patients with ESRD often experience extreme fatigue, a medical condition that may have serious consequences for their overall health. Exhaustion may be caused by several different things, such as uraemia, anaemia, malnutrition, inflammation, comorbidities, and a lack of physical activity. Socio-demographic factors such as education and social networks can also contribute. Issues with mental health and behaviour were cited, including insomnia, anxiety, depression, stress, and substance addiction. Symptoms of dialysis include fatigue after treatment, dialysis method, treatment efficacy, and treatment frequency.[7]

ESRD may affect not only the patient, but also their loved ones. Parental roles might shift as a result of a number of changes within the family dynamic. If a patient with ESRD who is also a parent is unable to fulfil their duty, they may experience a deterioration in self-esteem or self-image. Finally, having a parent who is chronically ill is likely to affect the family's efficiency and their sense of identity. A person with ESRD may feel like they are failing themselves or others when they do not meet their own or others' expectations. Systems theory suggests that as parents' roles change, they may feel a decline in self-esteem that might affect their marriage and family life.[8]

OXIDATIVE STRESS AND END-STAGE RENAL DISEASE

Due to an unfavourable ratio of antioxidant defence to reactive oxygen species production, oxidative stress develops. Antioxidant insufficiency is common in those with ESRD. At the same time, ageing, diabetes, cardiovascular disease,

inflammation, and the bio-incompatibility of dialysis membranes all contribute to a rise in oxidant activity. Patient outcomes are increasingly at risk from oxidative stress.[8]

PSYCHOTHERAPEUTIC CHARACTERISTICS IN END-STAGE RENAL DISEASE

Patients on dialysis have benefitted from psychological therapy. The therapy's ends would shift depending on the individual's history and current mental state. Individual or group treatment sessions were conducted. There have been several studies done in India that have shown the efficacy of psychotherapy in treating a wide range of persistent medical issues; however, there is a lack of research on ESRD.[9] Many psychotherapies and strategies are utilised to alleviate the psychological difficulties in ESRD, including cognitive behavioural therapy.[10] This has shown to be useful in the treatment of clinical depression and anxiety in patients with long-term health problems. Behaviour modification and counselling are also used to bring about desired alterations in one's health-related ways of living.

Similarly, psycho-education is a widespread kind of intervention used in hospitals for a variety of medical disorders. Brief sessions would focus on the most pressing emotional, social, economic, and physical concerns related to the disease. Dependent upon the nature of the issue at hand, family members or others considered important may also be invited to participate in the sessions. It is also common practice for counsellors to address the most frequently mentioned or observed psychological concerns while treating a patient. Adherence, quality of life, morbidity, and death are all predictably affected by psychological therapies in patients with ESRD.[11]

MECHANISM OF CEREBRAL DISEASES IN PATIENTS WITH END-STAGE RENAL DISEASE PATIENTS

There is a complicated relationship between the kidneys and the brain, known as the

'kidney–brain axis', which contributes to the high incidence of brain abnormalities in patients with ESRD.[12] Similarities in the anatomical and vasoregulatory structures of the brain and kidneys suggest that these two forms of vascular disease may have the same pathogenesis.[12] Brain MRI studies have demonstrated structural abnormalities in patients with ESRD.[13] Compared to healthy adults of the same age, patients with ESRD had a higher prevalence of white matter lesions, silent infarcts, brain atrophy, and axonal demyelination. In order to better understand the functional impairments of brain networks in patients with ESRD, rs-fMRI has recently emerged as a promising approach.

Based on the blood-oxygen-level-dependent principle, rs-fMRI data may be analysed to uncover temporal synchronisations between distant brain areas, commonly known as functional connectivity.[14] Depending on the method of analysis, functional connectivity alterations in patients with ESRD may exhibit a wide range of complexity. DMN connectivity impairment in the posterior cingulate cortex, precuneus, and medial prefrontal cortex, or decreased activity in a diffuse pattern across bilateral frontal, parietal, and temporal lobes were found in rs-fMRI studies of patients with ESRD before dialysis was mentioned. In the years thereafter, researchers have identified a handful of symptoms that contribute to decreased connectivity in patients with ESRD. Patients undergoing haemodialysis (HD), a procedure that necessitates the use of complex cognitive behaviour planning, have been demonstrated to have reduced connectivity in the anterior cingulate cortex. Evaluating global functional connectivity revealed abnormal intrinsic dysconnectivity in salience network regions spanning the contralateral insula and dorsal anterior cingulate cortex in patients with ESRD undergoing HD. However, the majority of the aforementioned ESRD studies only included individuals undergoing HD, who had mild-to-moderate cognitive impairment.[15]

URAEMIC TOXINS AND NEUROLOGICAL DISEASE

Uraemic CKD is characterised by the retention of potentially harmful solutes such as urea, creatinine, parathyroid hormone, myoinositol, and 2-microglobulin. The notion that one or more of these retained toxins influence neurological dysfunction in CKD has been the subject of several studies examining the pathophysiology of neurological disease in CKD.[16] Clinical symptoms and nerve conduction parameters improved rapidly following kidney transplantation, often within days of surgery, and were demonstrated to be inversely related to the severity of renal impairment. The rapidity with which these changes take place suggests that toxin-mediated inhibition of neuronal transmission plays a substantial role in the neurological dysfunction seen in CKD.

CENTRAL NERVOUS SYSTEM COMPLICATIONS

Encephalopathy
Renal failure often leads to encephalopathy, which may be caused by a wide range of conditions such as uraemia, thiamine deficiency, dialysis, transplant rejection, hypertension, fluid and electrolyte imbalances, and pharmaceutical toxicity. Confusion, disorientation, and finally coma and delirium, are typical symptoms of encephalopathy. Seizures, chorea, asterixis, multifocal myoclonus, and tremors are among the symptoms that accompany this disorder. These signals shift on a daily, and sometimes an hourly basis.[17]

Dementia
Patients with renal failure are at an increased risk of developing dementia. It is expected that 4.2% of elderly dialysis users will develop dementia, most often multi-infarct dementia. It is anticipated that 3.7% of this cohort will get multi-infarct dementia, making it 7.4 times more common than in the overall older population. The unfavourable profile for cerebrovascular disease in these individuals explains this.

Depression and delirium are also prevalent issues in renal failure, but they should be treated differently. Dialysis dementia and progressive multifocal leukoencephalopathy are two examples of subacute and rapidly progressing forms of dementia. Patients with chronic renal failure often have cerebral atrophy, and this is the case even in those without overt mental or emotional deterioration. On the other hand, intellectual deficiencies are often revealed via the use of psychometric testing.[18] Possible causes of the shrinkage include atherosclerotic brain damage, arterial hypertension, and endogenous uremic toxins.

Cerebrovascular Disease

Patients with renal failure are at increased risk for developing cerebrovascular disease, a primary cause of mortality in this patient group. This population is at a higher risk for developing atherosclerosis and having an ischaemic stroke. However, the possibility of experiencing haemorrhagic complications is elevated by a number of risk factors. Ischaemic stroke due to renal failure is most often caused by atherosclerosis, thromboembolic disease, and intradialytic hypotension.[19] Atherosclerosis is more prevalent and more distantly situated in individuals with chronic renal failure than in the general population. Traditional atherogenic risk factors, such as male sex, age, diabetes, hypertension, dyslipidaemia, and smoking, and variables specific to renal failure and its treatment certainly contribute to this. Renal failure has been linked to or may be related to hyperhomocysteinaemia, problems in calcium-phosphate metabolism, a buildup of guanidino chemicals, and oxidative and carbonyl stress.

Osmotic Myelinolysis

Individuals with renal failure often have osmotic myelinolysis in the central basis pontis, while it may also occur in the midbrain, thalamus, basal nuclei, and cerebellum. Central pontine myelinolysis is characterised by acute progressive quadriparesis, speech and swallowing problems, altered states of consciousness, and other neurological symptoms. When the demyelination spreads to the middle of the brain, it paralyses both the horizontal and vertical movements of the eye muscles. When the cerebellum or the basal nuclei are damaged, the result might be either Parkinson's disease or ataxia.[20] Hyperintense demyelination patches are seen on T2-weighted MRI scans. In many cases, death is inevitable, and even for those who do make it through, full recovery may take months. Only comfort measures are taken. Considering the unproven pathophysiology, it is prudent to treat chronic hyponatraemia gradually while avoiding hypernatraemia.

Movement Disorders and Restless Legs Syndrome

Renally compromised patients may have trouble moving because of encephalopathy, medicine, or anatomical abnormalities. Involuntary motions come in several forms in metabolic encephalopathy. Clinically, asterixis, also known as 'flapping tremor', consists of multifocal action-induced jerks that, in extreme situations, might pass for drop attacks and are likely produced by an abrupt loss of tonus originating in the cortical region. Myoclonus is characterised by sudden, involuntary, and often painful muscular spasms. These cramps vary in frequency and intensity and are followed by brief periods of calm. Myoclonus of action may arise on its own in uraemia, and the condition responds well to benzodiazepines when it does. It has been hypothesised that uremic myoclonus results from a water-electrolyte imbalance, which in turn causes microcirculatory and degenerative alterations in the lower brainstem reticular formation.[21] The uremic 'twitch-convulsive' syndrome is characterised by severe asterixis and myoclonic jerks, along with fasciculations, muscular twitches, and seizures; it is a common movement condition in uremic encephalopathy. The malfunctioning of the basal ganglia due to thiamine shortage is regarded to be the final cause of chorea.

Opportunistic Infections

Early diagnosis may be challenging since the conventional indications of infection are muted in immunosuppressed

individuals, and they are also more likely to get infections from rare and unusual opportunistic pathogens. Treatment of the infection with antibiotics and reducing dosage of immunosuppressants needs to be begun quickly. Acute, subacute, and chronic forms of neurological infections including meningitis, encephalitis, myelitis, and brain abscess are common in patients with renal failure. Many different types of bacteria may cause opportunistic infections; some well-known examples include *Nocardia asteroides, Mycobacterium tuberculosis*, and *Listeria monocytogenes. Aspergillus fumigatus*, *Candida albicans, Pneumocystis carinii, Histoplasma capsulatum, Mucor spp., Paracoccidioides,* and *Cryptococcus neoformans* are all examples of common fungi.[22] Reactivation of latent viruses is very uncommon; however, it may happen with herpes simplex virus, cytomegalovirus, and JC polyomavirus. Cytomegalovirus infection is the most common opportunistic infection after kidney donation. Invasive types may cause meningitis, encephalitis, myelitis, and nerve root involvement, but often cause no symptoms at all. Progressive multifocal leukoencephalopathy is caused by JC polyomavirus reactivation and infection of oligodendrocytes. Symptoms include a fast deterioration into a vegetative state, as well as dementia, ataxia, visual abnormalities, and other focal neurologic impairments. Currently, there is no proven therapy regimen, and all others are in the early stages of development. Infections caused by the metazoan *Strongyloides stercoralis* and the protozoan *Trypanosoma cruzi* have both been identified.

Neoplasms

Immunosuppressed patients with renal failure are more likely to get opportunistic infections and develop *de novo* malignancies. Patients with ESRD have been observed to develop malignant meningioma and primary central nervous system lymphoma. Lymph proliferative illness is more common in those who have had kidney transplants and subsequently underwent immunosuppressive medication. The Epstein-Barr virus is present in the majority of lymph proliferative diseases that develop after a transplant. There

is a high mortality rate associated with this illness, which affects 1–2% of renal transplant recipients. The localisation of post-transplant lymphoproliferative disease has evolved over time in response to modifications in immunosuppressive protocols. Before cyclosporine was used, the illness most often manifested itself in the central nervous system.[23]

The introduction of cyclosporine increased the frequency of presentations in the thorax and abdomen. There is not yet an accepted treatment standard for post-transplant lymphoproliferative disease. Allograft rejection is more common when immunosuppressant dosages are decreased or stopped altogether. Radiation treatment is often used to treat disorders of the brain and spinal cord. Combinations of acyclovir with surgery, chemotherapeutic drugs, and monoclonal anti-lymphoma immunotherapy have shown to be effective.

Intracranial Hypotension

Patients with orthostatic headache, especially those with associated neck stiffness, nausea, visual problems, dizziness, hearing loss, or abducens nerve palsy, should be evaluated for intracranial hypotension. Early detection is crucial for successful treatment of subdural hematoma with bed rest, increased fluid intake, and steroids. Imaging evidence of brain descent is common, as is diffuse pachymeningeal gadolinium enhancement on MRI of the head. The absence of activity across the cerebral convexities is evident on radioisotope cisternography, even after 24 or 48 hours, and the degree of the leak is occasionally disclosed in these cases. The pressure of the spinal fluid may establish a diagnosis. The disease may arise on its own, as a result of a cerebrospinal fluid leak, or, less often, in cases of dehydration and uraemia.[24]

Intracranial Hypertension

There are a number of potential triggers for intracranial hypertension in patients with chronic renal failure, including but not limited to idiopathic causes, secondary causes (such as dialysis or steroid use),

and intracranial abnormalities (such as neoplasm, infection, or cerebrovascular disease). Diagnosis of pseudotumor cerebri, also known as idiopathic intracranial hypertension, is made when patients present with symptoms related to excessive intracranial pressure despite normal neuroimaging findings (excluding any non-specific evidence of raised intracranial pressure). Increased pressure may appear clinically as headache, transient vision impairment, and diplopia due to unilateral or bilateral sixth nerve palsy. Examples of non-specific symptoms include dizziness, nausea, vomiting, and tinnitus. The increasing pressure within the skull affects the optic nerves, leading to papilledema and progressive optic atrophy, which in turn causes a narrowing of the visual field, a loss of colour vision, and eventually blindness. To prevent vision loss due to increased intracranial pressure, the treatment goal is to manage the underlying renal sickness and, if possible, to use acetazolamide, furosemide, or corticosteroids. Fenestration of the optic nerve sheath, lumboperitoneal, ventriculoperitoneal, or ventriculoatrial shunting surgery may be necessary in individuals whose vision continues to deteriorate after maximum medicinal treatment.[25]

NERVOUS SYSTEM COMPLICATIONS

Mononeuropathy

In uraemia, the nerves in the limbs are more susceptible to compression and local ischaemia. The ulnar, median, and femoral nerves are the ones often affected by this disorder. It is possible for the ulnar nerve in the wrist to be damaged by uraemic tumoral calcinosis, which may manifest in Guyon's canal. Motor dysfunction with paresis of intrinsic hand muscles, sensory loss in the hypothenar eminence, the little finger, and the lateral region of the ring finger, or a combination of these, are all possible outcomes. Electromyography and nerve conduction studies may verify the site of entrapment and provide evidence of the disease's severity. If anti-inflammatory medicines, tricyclic antidepressants,

anticonvulsants, and splinting don't help, or if motor deficits develop, neurolysis surgery may be the next best option.[26]

Polyneuropathy

Uremic polyneuropathy affects the nerves throughout the body, including the motor, sensory, autonomic, and cranial nerves, and affects around 60% of people with chronic renal failure.[27] The condition manifests itself clinically as asymmetrical distal sensory loss across all modalities, with a greater emphasis on the lower limbs, and a male predilection for reasons that are not fully understood. Most peripheral nervous system injuries can be prevented if the glomerular filtration rate is approximately greater than 12 mL/min. Below this threshold (approximately 6 mL/min), abnormalities in nerve conduction tests and clinical signs of peripheral nerve injury become apparent. The inability to feel vibrations as strongly and a general reduction in temperature sensitivity are early warning signs. There is a widespread presence of contrasting sensations of heat, cold, pain, and tingling. Areflexia, restless legs, muscle weakness, cramping, and atrophy, and increasing hypesthesia to pinprick or touch are all possible late-stage symptoms. In most situations, neuropathy develops over the course of several months. Common side effects of renal failure and dialysis include itchy skin. There is a dearth of understanding about its origin. Autonomic neuropathy has been linked to a wide range of symptoms, including intravascular and orthostatic low blood pressure, incontinence, diarrhoea, constipation, oesophageal dysfunction, hyperhydrosis, and impotence. A battery of cardiovascular autonomic testing should include measurements of heart rate variability while resting flat, breathing deeply, and doing the Valsalva manoeuvre.[27]

Myopathy

Uraemic myopathy is a disease often seen in patients with ESRD but its exact nature is still up for discussion. Individuals with chronic renal failure may present with a range of musculoskeletal abnormalities, including both functional

and anatomical alterations, due to their uraemic illness. Uraemic myopathy is a common complication in patients with a glomerular filtration rate of <25 mL/min, and it often increases in parallel with the patient's diminishing renal function. Dialysis patients as a whole make up an estimated 50% of cases.[28] It causes fatigue quickly, and weakness in the upper and upper-mid body. Electromyography and muscle enzyme tests, as well as a physical examination, all come up negative. Atrophy of the fibres, most often the Type II fibres, may be seen on a muscle biopsy rarely. As uraemic myopathy progresses, it may lead to cardiomyopathy. As there is currently no cure for uraemic myopathy, it is crucial to avoid it with regular dialysis treatments, ideally with high-flux membranes.[29] In addition, recombinant human erythropoietin for the treatment of renal anaemia and aerobic exercise training for the prevention of secondary hyperparathyroidism, as well as dietary adjustments, may be required. Supplemental I-carnitine has had mixed reviews in the scientific literature.[30] Certain subsets of dialysis patients might see significant improvement after taking supplements. Within 2 months of a successful kidney transplant, patients have a dramatic decrease in their complaints, while their physical functioning is not totally restored.

CONCLUSION

The number of people who are diagnosed with ESRD is rising rapidly over the globe. Many people on chronic dialysis struggle with exhaustion, which negatively impacts their quality of life. Combating weariness is in the eyes of some patients, and it is just as crucial as staying alive. Struggles exist in reducing the weariness experienced by the dialysis population, despite its critical importance. There is a high rate of morbidity and mortality in individuals with renal failure due to neurological complications. Despite the ongoing advancements in therapy, many of the neurological effects of uraemia do not improve with dialysis, and in some cases, dialysis or kidney transplantation might even make symptoms worse. In order to provide patients with renal failure the best care possible, both neurologists and nephrologists need to be aware of the possibility of neurologic disorders. Working together across disciplines is crucial for effective disease prevention, early detection, and treatment. Functional connection was disrupted in some ways in patients with ESRD using peritoneal dialysis. The most noticeable changes were made to the DMN and salience networks, which both saw reduced and increased connection.

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