Neuropsychiatric disorders and renal diseases: an update

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Submitted on: 10/08/2013.
Approved on: 10/11/2013.

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DOI: 10.5935/0101-2800.20140056

Abstract

Neuropsychiatric symptoms are frequently associated to renal dysfunction and may compromise negatively the clinical course as well as the quality of life, and the functional status of the patients. The neuropsychiatric disorders associated with renal disease may present various forms according to the natural history of the disease, and remain underdiagnosed and undertreated. There are few data in the literature regarding the treatment of these patients, and a lot of controversies still exist. The objective of this paper is to describe the most frequent neuropsychiatric disorders in patients with renal diseases.

Keywords: acute kidney injury; anxiety; depression; kidney diseases.

Introduction

The psychiatric disorders associated with kidney disease take many forms, depending on the natural history of the disease. Classically, uremia has been cited as the cause of delirium.[1] Symptoms such as somnolence and psychomotor agitation may be present among the clinical signs of acute kidney injury (AKI).[2] Drug regimens should also be considered as a potential source of psychiatric disorders. Steroids and cyclosporine, used in the treatment of various glomerulopathies and administered subsequently to renal transplantation, have been associated with depression, mania and psychotic symptoms.[3]

As in every chronic condition, patients with chronic kidney disease (CKD) may suffer from limited functional capacity, impaired productivity, and reduced quality of life.[4] Psychiatric disorders are highly prevalent in patients with CKD. Kimmel *et al.*[5] showed that patients with CKD had to be hospitalized for psychiatric disorders (particularly depression, dementia, and substance abuse) 1.5 to three times more than individuals with other chronic diseases. Yet, they are still underdiagnosed and undertreated.[6]

This paper discusses some of the neuropsychiatric disorders often associated with kidney disease.

Neuropsychiatric disorders associated with kidney disease

Delirium

Delirium is an acute behavioral disorder caused by impaired brain activity, leading to cognitive impairment usually secondary to a systemic disorder.[7] It is a condition of abrupt onset, characterized mainly by decreases in the affected subject's level of consciousness, attention disorders, temporal/spatial disorientation, disorganized thinking, and fluctuation of symptoms throughout the day. Agitation, delusion, visual hallucinations, and mood swings may also occur. Changes in the patient's EEG are usually observed within the first 48 hours of onset of renal failure

and anomalous findings may persist for up to three weeks after the cessation of dialysis.[4]

Many are the predisposing factors for delirium in renal diseases. The causes of delirium may be common to other patients, and may include fever, hemodynamic instability, polypharmacy, hypo/hypernatremia, acid-base disorders, hypercalcemia, hyper/hypoglycemia, anemia and vitamin deficiency (thiamine and cyanocobalamin).[3] However, in patients with renal failure, some specific causes must be considered, such as uremia, aluminum toxicity, subdural hematoma (associated with anticoagulants and platelet dysfunction), and dialysis disequilibrium syndrome.[8]

Dialysis disequilibrium syndrome (DDS) is caused by a sudden correction in azotemia and a consequent change in pH and osmotic pressure, which produce a pressure gradient between the central nervous system and plasma, leading to cerebral edema. DDS may set in 3-4 hours after the start of dialysis and may last for 8-48 hours after the end of dialysis. It is a transient condition characterized by headaches, nausea, cramps, delirium, epileptic seizures, and coma.[4]

Early detection of delirium is of paramount importance, and treatment must be individualized for each patient.[9] Prevention is the first step when it comes to dealing with delirium. This can be done by identifying and treating predisposing factors and with early patient immobilization. There is no evidence to support the use of drugs in the prevention of delirium.

First-line treatment includes non-pharmacological approaches such as sleep facilitation, constant reorientation, sensory deprivation control, and pain management. Antipsychotics are commonly used to treat delirium both in hospital and intensive care unit settings. However, the scientific evidence to support the use of drug regimens to treat delirium is limited, and no medication has been approved to that end.[10] Although the pathophysiological models of delirium describe a dysregulation in cholinergic neurotransmission, the use of anticholinesterases is not recommended. In 2010, a trial on the use of an anticholinesterase to treat delirium had to be discontinued, as the drug failed to benefit patients and possibly caused them harm, as a tendency for higher mortality was observed in the treatment group.[11]

Uremic encephalopathy

The term uremia was first used in 1840 by Piorry and l'Heritier, to relay the view that the clinical signs of renal failure were related to toxicity by urea. Currently, uremia is described as a clinical syndrome associated with renal failure and accumulation of nitrogen compounds. However, no specific substance has been implicated to date.[12] Factors such as hormonal disorders, oxidative stress, accumulation of metabolites (such as guanidine compounds, kynurenine pathway metabolites), imbalance between excitatory and inhibitory neurotransmitters, and disorders of intermediary metabolism have been identified as possible contributing factors.[13] Uremic encephalopathy is more severe and progresses more rapidly in patients with acute deterioration of renal function.[14]

In addition to the symptoms present in delirium, in uremic encephalopathy symptoms may progress along a continuum, from mildly altered levels of consciousness to deep coma. Headache, visual disturbances, tremor, multifocal myoclonus, and epileptic seizures are frequently present. Clinical signs also fluctuate over hours or days.[13] Patients may experience progressive cognitive impairment over days to the day of diálise.[15] However, levels of azotemia (nitrogen compounds) have been poorly correlated with neurological disorders.[14]

Most symptoms resolve with renal replacement therapy - dialysis or transplantation.[16]

Cognitive alterations

Cognitive deficits in patients with chronic kidney disease are common but poorly recognized. The identification of deficits may have a positive impact on patient outcome, especially when they are secondary to depression or delirium, potentially treatable conditions that must be considered in the differential diagnosis of cognitive impairment.[17,18] Alzheimer's and vascular dementia in particular are commonly seen in patients with CKD, the latter due to

comorbidities with hypertension, diabetes and atherosclerosis.[19] Dementia has been associated with greater levels of disability, more deaths and hospitalizations, and interruption of dialysis.[5,17]

Patients on dialysis for more than a year may suffer from a progressive neurological syndrome called 'dialysis dementia', characterized by dysarthria, dysphagia, and global dementia with preservation of the level of consciousness. Individuals with dialysis dementia may die within 6-12 months if not treated properly. The most widely accepted pathophysiology of dialysis dementia revolves around toxicity of the aluminum salts found in dialysis fluids. The introduction of preventive measures (discontinuation of the use of aluminum salts in dialysis fluids and phosphate binders containing aluminum) led to a significant reduction in the number of cases.[4]

Major depressive disorder, recurrent depressive disorder, and suicide

Depressive disorder is the most frequently described psychiatric condition in patients with end-stage renal disease (ESRD).[6] Prevalence can be as high as 100%, depending on the criteria utilized and the population analyzed.[18] Two studies carried out in Brazil with patients on hemodialysis reported prevalences of major depressive disorder of 44.8% when the Beck Depression Inventory (BDI) was used and of 7.8% when the 10-item screening questionnaire of the Center for Epidemiologic Studies Depression Scale (CES-D) was applied.[19,20]

In a recent meta-analysis, patients on dialysis were reported to have higher rates of depression and increased risk of hospitalization due to psychiatric disorders than individuals undergoing conservative treatment and post-transplant patients.[5,21]

Among dialysis patients, subjects on peritoneal dialysis had a lower prevalence of depression, anxiety symptoms, and sleep disorders than individuals on hemodialysis.[22,23]

Notably, the presence of depression symptoms may adversely affect the outcome of patients with ESRD.[24] Possible consequences are reduced compliance to treatment, nutritional status deterioration, impaired immune system function, and higher death rates.[18,25]

Despite the significant prevalence of depression and the associated morbidity, most cases remain underdiagnosed and undertreated.[6,15] A significant portion of the somatic complaints associated with CKD - fatigue, anorexia, weight and sleep disorders - may mimic depression symptoms. It has been suggested that the presence of non-vegetative symptoms (depressed mood, suicidal thoughts, pessimism, hopelessness, guilt, and aboulia) would be more adequate in the characterization of depression.[4] Diagnostic screening scales such as the BDI and the CES-D appear to be useful for patients with CKD, given the high prevalence of depression and morbidities affecting this group of individuals.[26]

Patients with CKD are at a significantly higher risk of committing suicide than the general population, particularly in subgroups of subjects aged over 75 years, individuals suffering from alcohol and substance abuse, and patients recently hospitalized for psychiatric disorders.[27]

Few studies have looked into the treatment of depressive disorders for patients with CKD. Efficacy has been attributed to cognitive behavioral therapy (CBT) in terms of compliance to treatment and management of depression symptoms in patients with CKD. CBT has been recommended as an alternative or a complement to drug therapy.[15,26] Drug interactions and side effects (especially in transplant patients and subjects on immunosuppressants) must be considered when patients are offered medication for depression.[3] A more favorable side effect profile has turned Selective Serotonin Re-uptake Inhibitors (SSRIs) into the drug class of choice. Caution is needed when SSRIs are prescribed. Patients are usually started on a dose equivalent to 30% of what would be considered the usual dosage and must be monitored closely for response and signs of toxicity.[4,18]

Anxiety disorders

Anxiety is one of the most frequently diagnosed symptoms in patients with chronic disease.[15] However, the literature on the presence of anxiety disorders in CKD patients is still scarce.

Forty-five percent of 50 ESRD patients on dialysis were diagnosed with some form of anxiety disorder; 30% of them were not treated and had

persisting symptoms 16 months into follow-up.[28] Patients on hemodialysis have anxiety symptoms more frequently than individuals on peritoneal dialysis.[23]

A study carried out in Brazil with individuals diagnosed with familial glomerulonephritis and autosomal dominant polycystic kidney disease reported that this group of individuals had higher anxiety scores than subjects with other chronic conditions.[29] Another Brazilian study with 244 patients on hemodialysis reported that 5.3% of the subjects had social phobia.[30]

Very little has been said or written about the treatment of anxiety symptoms in patients with CKD. Thus, proposed therapies have been extrapolated from treatments offered to patients with anxiety disorders alone. CBT and SSRIs have surfaced as the treatments of choice.[31] Benzodiazepines should be avoided and used only in acute situations and for the shortest possible time, given their potential to cause dependence and associating with clinical complications such as delirium.[31] When needed, drugs with inactive metabolites, such as lorazepam and oxazepam, should be preferred. The cited benzodiazepines may have their half-lives quadrupled in ESRD patients and cannot be removed by dialysis. Thus, extreme caution is required when these medications are prescribed to patients with ESRD.[32]

Fatigue

Fatigue is one of the most common symptoms seen in patients with chronic disease, and may be observed in about 50% of adults and 25% of children and adolescents with CKD.[33,34] Among the factors possibly related to the development of fatigue are circulating endotoxins, inflammatory cytokines, and increased oxidative stress.[33] Fatigue has been positively correlated with depression, sleep disorders, and poor quality of life.[33,34] Moreover, fatigue has also been established as a predictor for cardiovascular events, independently from other known risk factors.[35] The approach to fatigue in CKD patients includes aggressive treatment of anemia, introduction of physical activity, and screening and treatment for depression.[36]

Conclusion

Despite the growing attention given to the psychiatric disorders of individuals with renal disease, patients still remain underdiagnosed and undertreated. Very few studies have been published on the treatment of neuropsychiatric disorders in this population, and doubts still hover over treatment effectiveness and safety. Early diagnosis is essential to enhance patient quality of life and improve the outcome of renal disease. Therefore, having a multidisciplinary team to care for patients with kidney disease is becoming increasingly important.

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