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THE BIDIRECTIONAL RELATIONSHIP BETWEEN KIDNEY DISEASES AND BRAIN DISORDERS

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ABSTRACT

The correlations between neurological and renal diseases have been increasingly described and studied, and both often involve vascular deterioration. The brain and kidney are connected by efferent sympathetic and afferent sensory nerves. Kidney damage that can lead to chronic renal failure is often related to vascular and neurological disorders, and impaired renal function can lead to vascular deterioration with cerebral microbleeding. Risk factors such as hypertension, ageing, diabetes, dyslipidemia, and obesity can all lead to vascular impairment, and neurological diseases can also be present in dialysis patients. In uremic encephalopathy, motor and mental dysfunctions can occur, with emotional changes and cognitive deficits. Uremia leads to elevated concentrations of inflammatory molecules and metabolic dysfunction, resulting in the degradation of muscle proteins. Protein catabolism generates toxic compounds which may be present in brain tissue, serum, and cerebral spinal fluid (CSF). Therapies are lacking in this field of research, although a slight positive effect has been observed with the use of antioxidants and anti-inflammatories. Here, we describe the bidirectional interrelationship between kidney diseases and neurovascular disorders. Further studies are needed to clarify several points regarding this interesting issue.

KEYWORDS: *kidney, brain, hemorrhage, neurology, vascular, metabolism, inflammation*

INTRODUCTION

Chronic kidney disease (CKD) is a major global health problem, affecting approximately one in ten adults (1). It is defined as decreased kidney function lasting at least three months and associated with a range of health problems from mild kidney damage to end-stage disease. Many patients with acute kidney injury frequently develop neurologic dysfunction that increases with chronic renal failure (2). Renal insufficiency causes central and peripheral nervous system disturbances in multiple ways, such as cognitive decline and cerebrovascular events; crosstalk vectors are thought to include hormones, baroreceptors, osmoreceptors, and direct organ innervation (3).

There is strong evidence that CKD is related to intracerebral hemorrhage (4, 5), suggesting a close relationship between stroke and CKD. Patients with vascular impairment, such as that occurring in strokes, have a higher incidence of CKD (6, 7). One study showed that about 30% of patients undergoing hemodialysis showed mental impairment, of

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which 8% showed severe symptoms (8). For example, in uremic encephalopathy, there may be motor and mental dysfunctions such as emotional changes, depression, and cognitive and memory deficits, but also more serious problems, including suicidal thoughts, confusion, tremors, delirium, psychosis, loss of muscular tone, seizures, coma, and death.

It is well known that the brain nerves control the kidney in physiological and pathophysiological conditions, but it is not clear how this mechanism occurs. Renal innervation plays an important role in regulating the hemostasis of body fluids. The brain and kidney are connected by efferent sympathetic and afferent sensory nerves. The efferent nerves are involved in regulating renal function, such as sodium reabsorption and glomerular function, while the afferent nerves modulate cerebral sympathetic blood flow (9) (Fig. 1).

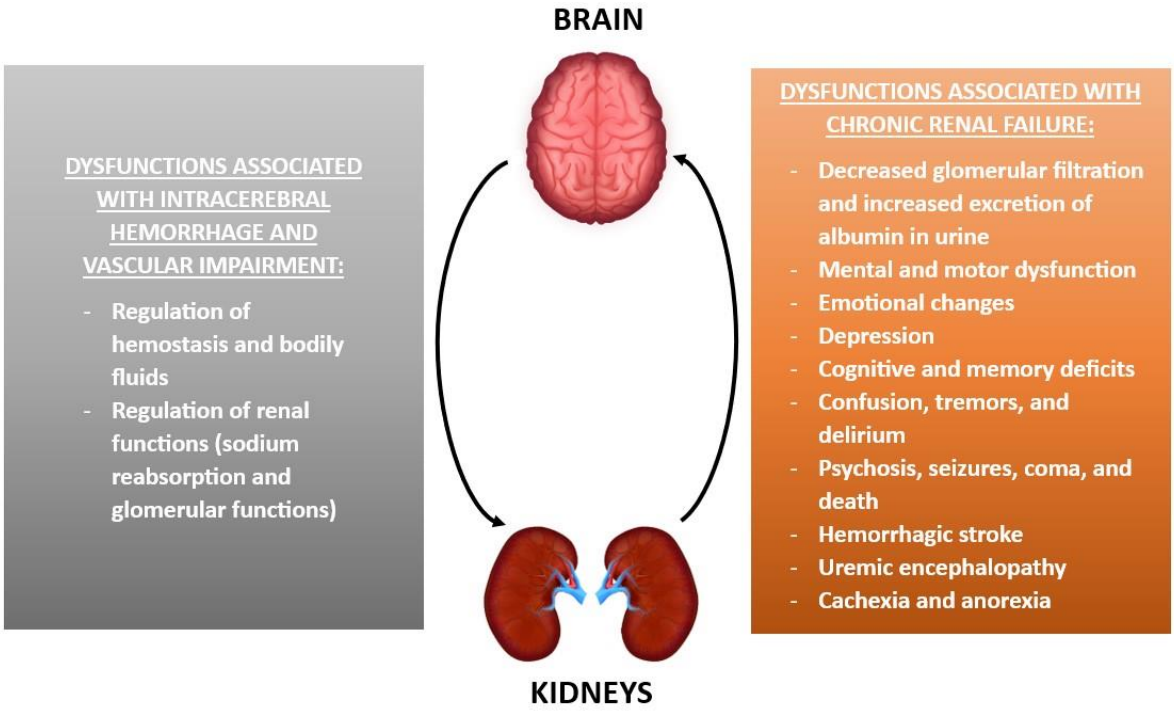

Fig. 1. *Correlation between the kidneys and brain. Chronic renal failure may lead to several mental dysfunctions. On the other hand, brain dysfunctions such as intracerebral hemorrhage and vascular impairment may cause dysregulation of renal function, hemostasis, and body fluids.*

DISCUSSION

Several metabolic diseases, such as hypertension, are due to chronic activation of the sympathetic efferent nerves of the kidney (10). In fact, via the renal sympathetic nerves, the autonomic nervous system allows kidney function to be adjusted dynamically in response to changes from all the visceral organs (11). Neurological and renal diseases are increasingly described and studied and often share vascular deterioration (12, 13). For example, cerebral microbleeds may be associated with impaired renal function (14, 15). Analysis of published research demonstrates a bidirectional relationship between brain disease and renal pathophysiology (16-19). Considering kidney diseases, a relationship between these and brain dysfunctions is highlighted, even if the studies can be very heterogeneous and, therefore, have a certain variability (19). Therefore, there seems to be an association between the physiological state of the kidney and brain diseases related to small vessel dysfunction and cerebral hemorrhage. This disease has a high pathogenicity due to a lack of effective therapy, so prevention, such as blood pressure control, is very important. Angiotensin II is central in this mechanism, acting as a neuromodulator or neurotransmitter. Its effects are hemodynamic, regulating blood pressure, and non-hemodynamic, maintaining the water-electrolyte balance.

In addition to sharing the same cerebral pathophysiological mechanisms as cardiovascular disease, it has been reported that cardiovascular risks may be higher in individuals with kidney disease (20). Kidney and neurovascular diseases, including stroke, are common risk factors (21). The traditional risk factors such as hypertension, ageing, diabetes, dyslipidemia, and obesity can lead to vascular impairment and endothelial dysfunction, as occurs in

cerebrovascular diseases such as stroke, white matter lesions, silent brain infarction, and microbleeds. In addition, risk factors such as stress, sympathetic nerve overactivity, chronic inflammation, and impaired coagulation, amongst others, contribute to vascular disease and endothelial dysfunction in the brain in patients with CKD. There is a higher risk of CKD after hemorrhagic stroke (22), although this needs to be confirmed by additional studies. However, the data on renal dysfunction linked to a higher incidence of cognitive impairment is often conflicting. Moreover, there seems to be a correlation between some kidney diseases and brain responses (23), but conversely, also between brain diseases (especially involving small vessel rupture) and kidney dysfunction (17).

In CKD, there is a decreased glomerular filtration rate and increased excretion of albumin in the urine, contributing to cerebrovascular risk (24). The presence of albuminuria has been reported as an independent factor of greater stroke risk, but it has not yet been well established if there is a greater risk of stroke with progressively higher levels of albuminuria (25). In fact, CKD is a risk factor for stroke (24) and other brain pathologies with impaired cognitive function (26). In kidney disease, uremia is related to sodium and water retention, uremic toxins, anaemia, calcium and phosphate metabolism dysfunction (hyperparathyroidism), and other anomalies. Hypoalbuminemia may occur in uremia, leading to cardiovascular risk in dialysis patients (27). Impaired albumin levels are associated with the release of acute phase proteins such as fibrinogen, C-reactive protein, serum amyloid A and P (28, 29), ferritin, ceruloplasmin, and others, all markers of inflammation. All these pathophysiological alterations can lead to cerebrovascular disease. Moreover, reduced albumin synthesis can cause anorexia with loss of body weight and muscle mass (30).

Uremic encephalopathy, an organic brain disease that can develop in patients with acute and chronic renal failure, can lead to pathologies ranging from mental disorders to death (31). Among patients with end-stage renal disease, nervous system dysfunction is a major cause of disability; those patients may develop sensorial clouding, delirium, tremor, asterixis, multifocal myoclonus, and coma. These patients can also develop peripheral neuropathy and progressive intellectual dysfunction (32). Elevated concentrations of inflammatory cytokines associated with cachexia, anorexia, and other dialysis-related disorders may occur in uremia (33, 34). In uremia, various metabolic dysfunctions occur, such as acidosis and resistance to insulin with consequent degradation of muscle proteins, an effect mediated by caspase activation (35). The inhibition of this molecule could represent a therapeutic target.

Neurological complications can occur in uremia and include concentration disturbances, mood alterations, headache, sleep disturbances, movement alterations, epileptic seizures, and coma (2, 36). This brain pathology is mediated by guanidine compounds such as guanidine-succinic acid, guanidine, methyl guanidine, and creatine (37). These compounds are waste products of protein catabolism, which are elevated in brain tissue, serum, and cerebral spinal fluid (CSF) after a uremic state (37). The alteration of calcium and phosphorus homeostasis, regulated by the parathyroid hormone (PTH), can mediate encephalopathy caused by uremia (38). These effects damage neurons and increase levels of neuropeptides that stimulate immune cells and increase inflammation (39, 40). These metabolic dysfunctions involving monoamines cause norepinephrine reduction and dopamine inhibition with motor activity dysfunction (41).

Uremia and the consequent malfunctioning of neurons can be increased by the metabolites of some drugs (such as cimetidine), which inhibit organic anion transporters (OATs), causing neurotoxic crises (42). OATs are normally localized in epithelial barriers and are involved in the uptake and intracellular movement of metabolites, drugs, and toxins (43 Nigam). In uremic encephalopathy, increased calcium due to hyperparathyroidism promotes renal failure by altering calcium transporters in neurons which may become hyperexcited. In such cases, blood-brain barrier (BBB) dysfunction can occur with excessive tryptophan input and increased serotonin (44) leading to decreased appetite, acidosis, cachexia, and inflammation. Inflammatory cytokines such as IL-1, tumor necrosis factor (TNF), and leptin can mediate the release of neuropeptides involved in anorexia (45, 46). Leptin acts on the brain system and the hypothalamus, and one of the most important functions of this molecule is to regulate food intake and to modulate energy processes (47). Patients with renal insufficiency who are malnourished may have thiamine deficiency encephalopathy (48), an effect reversible with supplemental thiamine.

Dialysis dementia may occur in patients undergoing chronic hemodialysis, but in kidney transplantation patients, this dementia does not often occur, and cognitive functioning has been seen to improve following transplantation (49-51). In the case of severe encephalopathy with convulsions and seizures, symptoms can be relieved using anticonvulsant drugs such as anti-epileptics. Even after adequate dialysis therapy, patients may continue to be afflicted with nervous system dysfunction, such as weakness, peripheral neuropathy, and mental disturbances. The dialytic treatment of end-stage renal disease has been associated with two separate disorders of the central nervous system (CNS): dialysis disequilibrium and dialysis dementia (52), which is progressive, fatal encephalopathy; this can occur in some cases and is linked to aluminium phosphate which is transported in the CNS via transferrin, causing brain alterations; this can be avoided with the preparation of dialysate water by reverse osmosis. Chronic renal disorder can also lead to convulsions due to uremia and toxic substances causing encephalopathy.

Therapy

CKD often predicts bidirectional neurological alterations that may even be lethal due to a lack of specific therapy, an issue requiring more investigation. Special attention has been paid to antioxidants in the therapy of neurological, microbial, and tumor diseases due to their anti-inflammatory properties. For example, it has been reported that curcumin, a versatile ingredient used particularly in Asian food recipes, can prevent or delay the onset of neurological diseases afflicting the CNS (53). Curcumin effectively prevents negative ageing processes, depression, Parkinson's disease, Alzheimer's disease, autism, amyotrophic lateral sclerosis, and other brain diseases (53, 54).

CONCLUSIONS

There is a bidirectional relationship between kidney disease and brain diseases. Some pathological states of the brain can influence the kidneys and *vice versa*. These findings are very important for discovering new therapeutical approaches for treating CKD and intracerebral hemorrhage.

Conflict of interest

The authors declare that they have no conflict of interest.

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