

Advances in Research Related to Cognitive Impairment in Maintenance Hemodialysis Patients

Hezhou Cai, Liqun Chen*

Department of Nephrology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, 400016, China

*Corresponding author

Abstract: Cognitive impairment is much more prevalent in patients with end-stage renal disease than in the general population. The mechanism of cognitive impairment is unclear, and it is currently believed that in addition to uremic toxin damage, followed by chronic inflammatory factors and dialysis complications influence, vascular problems, and sleep disturbances are also key. Cognitive impairment can cause prolonged hospitalization and decreased quality of daily life, and in severe cases affect patient survival. Early identification, assessment, intervention, and treatment of cognitive impairment can be beneficial to patients. This article describes the current risk factors, assessment options, and treatment modalities related to cognitive impairment in maintenance hemodialysis patients.

Keywords: maintenance hemodialysis, cognitive impairment, risk factors, treatment

1. Introduction

Cognitive impairment (CI) is defined as an impairment in one or more of the areas of language, memory, executive function, visual space, computation, reasoning, and thinking. There are many risk factors for cognitive impairment, with age being the biggest risk factor, followed by gender, education level, a family history of cognitive impairment, and certain chronic diseases such as hypertension, hyperlipidemia, coronary heart disease, diabetes and cerebrovascular disease, chronic kidney disease, etc[1,2]. According to epidemiological surveys, the prevalence of Chronic Kidney Disease (CKD) in China is as high as 10.8%[3]. Studies have shown that CI is independently associated with kidney disease and is associated with an increased incidence of hyperalgesia, particularly in patients undergoing maintenance hemodialysis, where the incidence of CI is much higher than in the general population and the age of onset is generally younger, 30-60% of patients with CI have MHD[4]. In contrast, van Zwieten A et al showed that the prevalence of CI in patients with MHD was 79.40%[5]. A major depressive disorder diagnostic criterion is cognitive impairment, which is difficult to identify at an early stage. CI can progress to dementia, resulting in complete loss of self-care, increased hospitalization costs, and even death. According to one study, cognitive impairment increased the risk of all-cause mortality by nearly threefold when compared to normal individuals.[6]. Therefore, it is beneficial to identify, assess, intervene, and treat patients with early cognitive impairment. This article reviews the risk factors, assessment options, and treatment associated with cognitive impairment in patients with MHD.

2. Factors affecting cognitive impairment in patients with MHD

The mechanisms by which MHD causes cognitive impairment are unclear and are thought to be complex and multifactorial. Factors affecting cognitive impairment are divided into both conventional and unconventional risk variables..

2.1 Traditional factors

When compared to the general population, MHD patients also experience cognitive deterioration due to age, gender, education, cerebrovascular illness, and sleep issues. Age raises the likelihood of cognitive impairment in MHD patients. Age ≥ 40 years was discovered to be an independent risk factor for the development of CI in a study of young and middle-aged individuals with end-stage renal disease[7]. Secondly, in the population with mild cognitive impairment (MCI), women were found to

have a significantly higher frequency of non-amnesic MCI than males did.[8]. Also, due to the scoring method, the more educated people had better memory, calculation, and drawing abilities than the less educated people. A study of 2287 people over 60 years of age found a significant interaction between body mass index and height on cognitive function [9]. Whereas cerebrovascular disease is a direct factor in vascular dementia, although CI may make a stroke more difficult to diagnose, small vessel disease or an asymptomatic cerebral infarction may have a more subtle impact on the development of the stroke[10]. Among neurodegenerative mechanisms, some suggest that the colloid lymphatic system, which removes protein waste from the brain, is primarily active during sleep, indicating a connection between sleep issues and the onset of signs of neurodegenerative dementia[11]. According to estimates, between 44% and 95% of MHD patients experience some form of sleep disturbance, and maintenance hemodialysis patients experience worse sleep quality than healthy controls who are age- and gender-matched[12-13], and the causes of sleep disturbance in MHD patients are associated with uremic toxins causing pruritus or uremic restless leg syndrome in addition to a mood[14].

2.2 Non-traditional factors

In addition to traditional factors, there are non-traditional elements that need to be considered when calculating the likelihood that MHD patients would experience cognitive impairment.

2.2.1 Uremic toxin

Cognitive impairment may result from uremic poisons that are continually building up in the blood and brain. According to the chemical binding properties and molecular weight of proteins, uremic toxins can be included as three major toxins: small water-soluble, medium and large molecules, and protein-bound. The medium- and high-molecular and protein-bound uremic toxins, with the exception of the smaller water-soluble uremic toxins, cannot be entirely eliminated during hemodialysis, and some of them are suspected to have detrimental effects on the peripheral or central nervous system[15]. The hemodialysis procedure improves cognitive impairment in patients with acute high levels of uremic toxins at the beginning of dialysis in people with end-stage renal disease; however, the persistence of cognitive impairment during the lengthy maintenance dialysis phase raises the possibility that it may be connected to the fact that some neurotoxic substances are not effectively cleared by hemodialysis and that toxin accumulation causes cognitive impairment.[16]. The intact blood-brain barrier protects the generally healthy state, but in advanced CKD, this barrier is dysfunctional [17]. Increased levels of neuroactive mediators can then penetrate the blood-brain barrier and result in decreased brain permeability, which can impair cognition. Neuropeptide Y is linked to the emergence of neurodegenerative illnesses, such as Alzheimer's disease. In people with kidney disease at its last stages, blood concentrations of neuropeptide Y are higher [18]. Contrarily, there is a considerable reduction in blood levels of neuro-like active chemicals and an improvement in cognitive impairment in patients following renal transplantation [19], indicating that uremic toxins are a possible cause of cognitive impairment in individuals with MHD.

2.2.2 Serum Homocysteine (Hcy) Levels

Patients with MHD frequently have high homocysteine levels because of renal failure. GUOYi-dan[20] et al discovered that high serum Hcy was a significant risk factor for cognitive impairment in individuals with MHD in a study of 107 patients on maintenance hemodialysis. Hcy acts as an excitatory neurotoxic substance, and its intracranial accumulation significantly increases neuronal susceptibility to neurotoxic and oxidative damage. This increases neuronal damage and consequently cognitive impairment. However, the precise mechanism underlying the association between Hcy and cognitive impairment is unknown[21].

2.2.3 Dialysis complications: hypotension, hypoglycemia, heart failure, anemia

During hemodialysis, severe arrhythmias may be caused by excessive and rapid dehydration and electrolyte imbalance, and hypotension is more likely to occur. Repeated hypotension can cause a decrease in cerebral blood flow, inadequate cerebral perfusion, and thus brain damage. A decrease in cerebral blood flow during dialysis corresponds with ultrafiltration rate, volume, temperature, and PH, according to research by Polinder Bos et al [22]. Real-time analysis by Findlay MD confirmed that a decrease in cerebral arterial flow is strongly associated with deterioration in cognitive function [23]. In addition, because the dialysate does not contain glucose, glucose is removed from the blood during dialysis, or patients with concomitant diabetes are prone to hypoglycemia due to the inappropriate use of hypoglycemic drugs. Low glucose metabolism and cerebral hypoperfusion may result in neuroinflammation and oxynitride stress, which in turn may produce amyloid b deposition, cerebral

amyloid angiopathy, disruption of the blood-brain barrier, neuronal injury, neurodegeneration, and cognitive or memory loss [24].

Heart failure is a frequent side effect in MHD patients. Cardiovascular instability during dialysis is very closely linked to cognitive impairment [25]. According to a recent systematic study, over 43% of MHD patients with heart failure have cognitive impairment [26]. Although cognitive impairment due to heart failure is also associated with vascular pathology, the pathophysiological mechanisms are not clear.

Anemia is one of the most prevalent side effects among maintenance dialysis patients, and it has been linked to cognitive impairment. The prevalence of both anemia and cognitive impairment rises with advancing age [27]. Anemia leads to inadequate oxygen supply to the brain, which in turn affects brain tissue-related metabolism and thus alters cognitive function [28].

2.2.4 Chronic inflammation

Chronic inflammation-induced endothelial dysfunction can promote protein extravasation in blood vessels, leading to blood-brain barrier dysfunction and inflammation-induced neuronal damage, which is directly associated with cognitive impairment. High levels of hs-CRP, fibrinogen, and IL-1b in dialysis patients were found to be connected with cognitive impairment in an observational study [29]. However, there are no studies to support that cognitive function can be improved by treating inflammation.

2.2.5 Vascular lesions

In patients with MHD, the incidence of atherosclerosis is higher due to changes in hemodynamics, a micro-inflammatory state, and disorders of calcium and phosphorus metabolism brought on by renal failure. These complications include chronic ischemia and hypoxia in the brain, lacunar cerebral infarction, and even cerebral infarction. On the one hand, diabetes and hypertension associated with kidney disease can directly cause chronic atherosclerosis. On the other hand, however, renal failure also causes changes in hemodynamics, This causes lacunar cerebral infarction and even cerebral infarction, which result in chronic brain ischemia and hypoxia and cognitive impairment [30].

3. Assessment modalities for cognitive dysfunction

MHD combined with cognitive impairment is clinically insignificant. In a retrospective study of a dialysis cohort (n = 338), the mean age of patients with cognitive impairment was 71.2 years, with mild cognitive impairment (13.9%), moderate cognitive impairment (36.1%), and severe cognitive impairment (37.3%), but clinical signs of cognitive impairment were present in only 2.9% of patients [31]. To prevent the occurrence of cognitive impairment in dialysis patients, it is necessary to identify and assess patients with early cognitive impairment. The high prevalence of cognitive impairment in MHD patients not only prolongs the hospital stay and causes long-term care problems for patients' families, but also seriously affects the quality of life and survival of patients. Cognitive assessment scales commonly used in clinical practice include the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Modified Mini-mental State Examination (3MS), and the Saint Louis University Mental Status Examination (MMSE). Saint Louis University Mental Status (SLUMS) examination, Clock drawing task (CDT), etc. Patients with cognitive impairment with higher levels of education can continue to score within the normal cognitive range on the MMSE [32]. One study showed that for individuals with at least a college degree, any score below 27 was an indicator of an increased risk of being diagnosed with dementia or Alzheimer's disease [33]. 3MS scale compared to the MMSE scale: The 3MS scale is more useful than the MMSE scale in older adults who are concerned about cognitive decline [34]. The MoCA scale is more appropriate than the MMSE scale for detecting mild cognitive impairment in older adults [35]. In contrast, the SLUMS scale is currently considered to be more sensitive than the MMSE scale in identifying cognitive impairment [36].

4. Treatment of cognitive impairment in patients with MHD

The effectiveness of treatments to lessen the severity of cognitive impairment is not well supported by the available data, although promising approaches include cognitive or physical exercise, modifications to dialysis, and kidney transplantation.

4.1 Effect of different renal replacement therapy modalities on the cognitive function of dialysis patients

Peritoneal dialysis patients are generally better educated compared to hemodialysis. Neumann et al. used propensity score matching to create hemodialysis and peritoneal dialysis treatment cohorts (n=100), and after matching for age, education level, employment status, and co-morbidities, both groups showed improvement in cognitive function after one year of treatment, but the improvement was more pronounced in peritoneal dialysis patients[37]. In our meta-analysis, Peng Hongmei et al. found that renal replacement therapy improved the level of cognitive function in patients, with renal transplant patients having better cognitive function scores than hemodialysis and peritoneal dialysis patients, and peritoneal dialysis patients having better scores than hemodialysis patients[38]. Renal transplantation continues to improve neurochemical mediators, cerebral blood flow, white matter integrity, and cognitive function in patients [19].

4.2 Prevention and treatment of dialysis complications

MHD concomitant or complicating conditions such as hypertension, diabetes mellitus, disorders of calcium and phosphorus metabolism, and ectopic calcification of blood vessels are closely related to the development of cerebrovascular disease. Hu Yanyi et al [39]. provided MHD patients with pharmacological interventions including active correction of anemia and control of blood pressure and other dialysis complications in addition to psychological interventions, and the MoCA scores of patients improved significantly after 6 months and were positively correlated with hemoglobin levels. Currently, active control of blood pressure and blood glucose and correction of calcium and phosphorus metabolism disorders in MHD patients may be one of effective ways to delay cognitive decline.

4.3 Treatment

There are no pharmacological treatments that effectively target patients with cognitive impairment. Depression is associated with cognitive impairment. The combination of cognitive behavioral therapy and sertraline is recommended for the treatment of depression in the general population, from which it can be inferred that treatment with cognitive behavioral therapy and sertraline is attempted in dialysis patients with cognitive impairment, but there are no conclusive recommendations for such attempts and it is not clear whether cognitive function improves in patients with MHD [40-42].

5. Conclusion

In conclusion, cognitive impairment has a high prevalence in MHD patients and causes great inconvenience to patients' life and work, increases the financial burden of patients' families, and even affects patients' survival rate. In this paper, we hope to improve the quality of life and survival of dialysis patients through early detection and prevention, and early intervention of factors that trigger cognitive impairment in dialysis patients from the perspective of pathogenesis and risk factors. We hope to provide some new ideas or methods for clinicians' diagnosis and treatment, but the pathogenesis of cognitive impairment in maintenance hemodialysis is still not clear, and further research is needed in the future.

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