

Structural brain changes in patients who receive different durations of hemodialysis

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Abstract

Background: Hemodialysis patients are particularly vulnerable to cerebral vascular disease. Both hemodialysis duration and cerebral small vessel disease are crucial in this patient population, and additional research is necessary to further understand their relationship.

Objectives: This study aimed to investigate the structural brain changes in patients who receive different durations of hemodialysis.

Methods: We recruited a total of 80 hemodialysis patients and categorized them into two groups to scrutinize the effects of hemodialysis treatment. Group 1 included 41 patients who received hemodialysis for more than six months, and Group 2 consisted of 39 patients who underwent hemodialysis treatment for less than six months. The structural and vascular modifications of the brain in these two groups were studied using a 1.5 Tesla MRI machine to perform brain scans by our research team.

Results: Patients who underwent hemodialysis treatment for a more extended period, with a median treatment duration of up to 4 years, showed minor vessel disease, compared to those who received hemodialysis for a shorter period of 3 to 5 months. The ischemic effects were predominantly found in areas such as the pre-ventricular, subcortical, and white matter, with mean±SD of 1.33±0.471, 1.23±0.420, and 1.39±0.490, respectively. Additionally, we identified other brain abnormalities, such as pons irregularities, global brain atrophy, thinning in the corpus callosum, and frontal lobe atrophy, with a significant value of $P<0.01$.

Conclusion: The study indicates that extended periods of hemodialysis reveal discernible signs of subcortical and periventricular white matter disease among patients. This finding provides critical insight into the potential long-term impacts of hemodialysis treatment, highlighting the need for further investigation and advanced treatment measures.

Keywords: Hemodialysis, Renal dialysis, Hemodialysis duration, Brain injuries, Magnetic Resonance Imaging (MRI)

Introduction

Chronic kidney disease (CKD) is a crippling illness characterized by a progressive deterioration in kidney function over time, eventually leading to end-stage renal disease (ESRD).¹ ESRD is a chronic condition that irreversibly damages the kidneys, thereby requiring hemodialysis (HD) as an alternative treatment. HD is a

complex medical procedure that necessitates frequent hospital or dialysis center visits, typically three times a week.² Overall, HD is the most commonly used treatment option worldwide, including in Iran. Notably, in 2013, over 1,500,000 individuals globally and 25,000 Iranian patients received HD. Such statistics highlight the growing prevalence of CKD and underscore the need for enhanced

awareness, early detection, and innovative therapeutic measures.^{3,4}

Various neurological abnormalities are associated with HD.⁵ Prior research indicates that subcortical areas in patients undergoing HD are vulnerable to damage commonly prevalent in the general population with vascular dementia.^{6,7} Furthermore, patients with renal failure are demonstrated to have a higher likelihood of experiencing structural brain injuries such as cerebral stroke and atrophy.^{8,9} These findings demonstrate the significant impact of HD on patients' neurological health and highlight the need to address the potential risks and consequences of prolonged HD treatment.

Neuroimaging plays a pivotal role in identifying neuropathological abnormalities, particularly for patients undergoing HD.¹⁰ In comparison to computed tomography (CT), magnetic resonance imaging (MRI) offers a more reliable assessment of abnormal brain signal intensity.¹⁰ Recently, structural and functional MRI techniques have helped identify models of neuropathological abnormalities in HD patients.¹¹⁻¹⁴ Brain MRI findings demonstrate that patients receiving long-term HD are more likely to experience neuroimaging issues, including white matter disease (WMD), cerebral atrophy, and overt or silent cerebral infarction.^{8,9,15} These findings have significant implications for therapeutic strategies and highlight the need for regular neuroimaging assessments in HD patients to improve therapeutic outcomes. Further research in this domain represents a crucial need for better therapeutic decision-making and improving patients' clinical outcomes.

Neuroimaging plays a pivotal role in identifying neuropathological abnormalities, particularly for patients undergoing HD. In comparison to computed tomography (CT), magnetic resonance imaging (MRI) offers a more reliable assessment of abnormal brain signal intensity.¹⁰ Recently, structural and functional MRI techniques have helped identify models of neuropathological abnormalities in HD patients.¹¹⁻¹⁴ According to brain MRI findings, individuals receiving long-term HD are more likely to develop neuroimaging abnormalities such as white matter disease (WMD), cerebral atrophy, and overt or quiet cerebral infarction.^{8,9,15}

White matter disease (WMD) is associated with a variety of negative outcomes in both the general population and HD patients, including overt cerebral infarction and an increased risk of cognitive impairment.¹⁶⁻¹⁹ Infarctions and WMD detected through brain MRI are linked to cognitive impairment and an increased risk of future clinical strokes, while cerebral atrophy and reduced hippocampal volume are connected to dementia.^{20,21} Multiple studies reveal that vascular diseases are among the leading causes of cognitive impairment in these patients.²² Nonetheless, the prevalence and clinical significance of stroke symptoms and vascular disease in HD patients remain poorly understood.

Objectives

The field of hemodialysis (HD) currently lacks specific neuroimaging results that can shed light on the neurological basis of cognition. Our study aims to address this by examining any structural brain changes in patients undergoing hemodialysis for differing periods of time.

Methods

Our study entailed enrolling 98 hemodialysis (HD) patients aged between 40 and 70, of whom 80 agreed to participate in the study. It is worth mentioning that individuals with a history of myocardial infarction, stroke, cerebral surgery, epilepsy, and depression were excluded from the research. The research was conducted in Iran's south-eastern city, Zahedan, at Ali-Ebne-Abi Talib and Khatamol-Anbia hospitals from 2016 to 2017. The HD patients were segregated into two groups: the first group had 41 patients who underwent HD for less than six months, while the second group had 39 patients who underwent HD for more than six months.

To investigate any structural brain changes in our HD patients, we employed a signal intensity ratio technique based on T1 and T2 imaging without contrast. Brain MRI images were collected using a 1.5 Tesla MRI device, specifically the Magnetom Vision Plus 1.5 Tesla by Siemens in Germany. We analyzed the axial T1, axial T2, and coronal FLAIR sequences of the brain MRI images.

We assigned an experienced radiologist to analyze the MRI images to investigate brain structural and vascular changes in both patient groups. To ensure unbiased

readings, the radiologist was unaware of the group assignment of the patients while analyzing the MRI images. The radiologist also prepared the MRI reports.

Study Protocol

We gave the Beck Depression Test to the patients before enrolling them in the trial to confirm that the study outcomes were not influenced by depression and that they were consistent with earlier findings. Specifically, we excluded patients who presented with depression, as previous studies have indicated that HD patients are at a higher risk of developing this condition.^{23,24}

To ensure that all patients were in similar physical conditions, we took blood samples prior to performing neuroimaging. We measured white blood cells, red blood cells, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets, red blood cell distribution width (RDW), mean platelet volume (MPV), platelet-large cell ratio (P-LCR), blood sugar, blood urea nitrogen (BUN), serum creatinine, sodium, potassium, calcium, alkaline phosphatase, and phosphorus.

Statistical analysis

The continuous variables were expressed as the mean \pm SD, and the categorical variables were presented as a percentage and frequency. A Shapiro-Wilk test was used to determine whether the data were normally distributed. We analyzed the cross-tables using Pearson's chi-square test. All statistical analyses were performed with SPSS (version 20.0, SPSS Inc, Chicago, IL, USA). A "P-value" less than 0.05 was considered significant.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki. The authors of this study have adhered strictly to ethical issues (such as plagiarism and data fabrication, as well as double publication). Each subject signed a consent form before they were admitted to the study. Ethics approval was also received from Zahedan University of Medical Sciences and the ethics committee (IR.ZAUMS.REC.1395.361). Also, during the study, patients would be excluded from research if they did not consent to continue participation.

Results

Table 1 presents the demographic and clinical data of 80 HD patients. Male HD patients had a higher incidence of cerebral vessel issues than female HD patients. Moreover, the number of right-handed patients was higher than left-handed ones. We also identified that HD patients who had completed middle school education had a greater likelihood of vascular problems than those who attained higher degrees of education. Notably, the mean age of HD patients with cerebrovascular problems was 52.4 ± 10.1 years.

Table 2 displays a significant association ($P < 0.05$) between periventricular abnormalities and the duration of HD treatment. The findings reveal that the rate of periventricular abnormalities in patients who received HD for less than six months was comparatively lower. Furthermore, the study found a link between HD treatment length and brain structure abnormalities such as subcortical, white matter, corpus callosum, periventricular, and global brain atrophy [Figure 1]. Notably, no correlation existed between HD duration and pones or frontal lobe impact in the participants.

Table 3 presents the mean values for frontal lobe and duration of HD variables, highlighting the highest and lowest scores as 50 ± 1.51 and 21 ± 1.05 , respectively. Furthermore, the study discovered a robust positive correlation between pons abnormality and the duration of HD treatment.

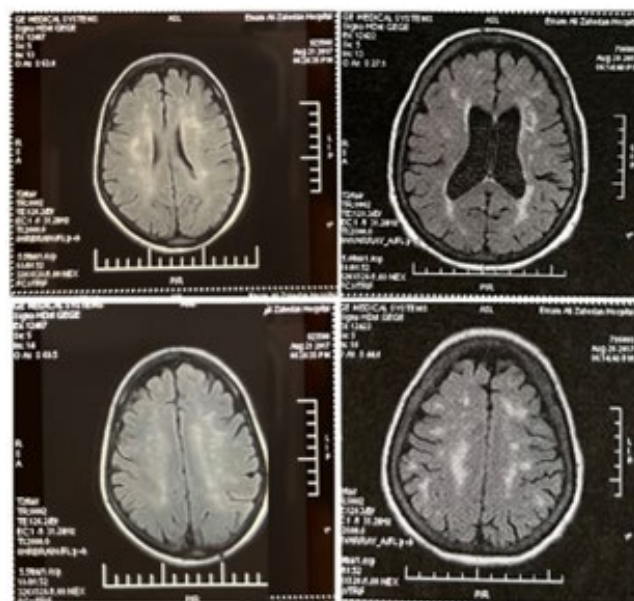


Figure 1. Subcortical, and periventricular white matter abnormality in long-term HD patients

Table 1. Demographic and MRI data of 80 HD patients

Variables		Brain MRI	
		No Vessel Problem	Vessel Problem
Sex	Male	35	26
	Female	14	5
Direct	Right	47	27
	Left	2	4
Education	middle School	21	15
	Diploma	15	9
	Associate	1	1
	Bachelor	10	6
	Master and upper	2	0
Age, year		50.7±8.11	52.4±10.1

Discussion

According to the study findings, individuals undergoing long-term HD treatment are more vulnerable to changes in brain structure, as demonstrated by periventricular white matter illnesses in the subcortical region [Figure 1]. Additionally, the study found a positive association between these structural abnormalities, lower levels of education, and older age. Moreover, men receiving HD treatment exhibit a greater likelihood of experiencing cerebral vessel problems relative to women.

In a systematic review and meta-analysis of several studies, it was found that men are more susceptible to moderate-to-severe cerebral small vessel disease-related

ischemic strokes. The reported prevalence in men was 62%, while in women, it was 38%.²⁵ Pavlovic et al. discovered that females with prior lacunar strokes had a higher severity of cerebral small artery disease, especially white matter hyperintensity, resulting in more cognitive deficits. The authors of this study highlighted that both sex and depression were significantly associated with the severity of white matter hyperintensities and the prevalence of depression.²⁶ Interestingly, one noteworthy aspect of our study is that depression was considered an exclusion criterion for participants. This was done to eliminate depression as a contributing factor to cognitive impairment, which helped isolate the role of HD treatment on brain structural changes. The results of this study suggest that men may be more susceptible to brain structural changes and associated cognitive impairments. Moreover, a recent systematic review and meta-analysis have revealed that individuals with a lower level of education are more likely to suffer from severe cognitive deficits due to small vessel disease.²⁷ In accordance with these findings, the present study suggests that patients with HD disease who have completed only middle school education are more likely to experience vascular problems, potentially indicative of a greater severity of structural brain changes.

Table 2. The number of patients who had vessel problem in the different part of their brains, based on HD duration

MRI		HD Duration		Mean±SD	df	P- Value
		<6Months (N=39)	>6Months (N=41)			
PVAB	NVP	35	19	1.33±0.47	1	0.000
	VP	4	22			
SCAB	NVP	36	26	1.23±0.42	1	0.002
	VP	3	15			
WMD	NVP	35	14	1.39±0.49	1	0.000
	VP	4	27			
PAB	NVP	35	38	1.09±0.28	1	0.472
	VP	4	3			
GBAT	NVP	39	36	1.06±0.24	1	0.031
	VP	0	5			
TCC	NVP	39	34	1.08±0.27	1	0.007
	VP	0	7			
FLA	NVP	39	37	1.05±0.21	1	0.064
	VP	0	4			

Abbreviations: PVAB, Periventricular Abnormality; SCAB, Subcortical Abnormality; WMAB, White Matter Disease; PAB, Pons Abnormality; GBAT, Global Brain Atrophy; TCC, Thinning of Corpus Callosum; FLA, Frontal Lobe Atrophy; NVP, No Vessel Problem; VP, Vessel Problem.

Table 3. The mean scores and correlation of brain parts and HD duration

Factors	1	2	3	4	5	6	7	8
HD Duration	1							
PVAB	0.463**	1						
SCAB	0.346**	0.777**	1					
WMAB	0.570**	0.872**	0.677**	1				
PAB	-0.052	0.068	-0.061	0.026	1			
GBAT	0.252*	0.262*	0.356**	0.219	-0.080	1		
TCC	0.302**	0.163	0.151	0.117	-0.096	0.468**	1	
FLA	0.224*	0.208	0.288**	0.288**	-0.071	0.652**	0.538**	1

* Correlation is significant at the 0.05 level (2-tailed), ** Correlation is significant at the 0.01 level (2-tailed)

As people age, chronic systemic inflammation can lead to numerous age-related diseases, including vascular diseases. This has become a concern, especially with the increasing number of people aging worldwide, as it contributes to the rise in stroke and vascular dementia cases. Moreover, research has demonstrated how inflammation and immune activation can exacerbate the pathogenesis of prevalent age-related diseases such as diabetes, atherosclerosis, and Alzheimer's disease, helping experts understand these diseases' root causes.^{28,29} This study provides additional insight into the issue as it found a possible correlation between cerebrovascular problems and age; HD patients in the study averaged 52 years old, which increases the risk of severe age-related problems to a higher degree.

Abnormal periventricular gradients in an otherwise normal-looking white matter can indicate various neurologic diseases and aging conditions. The study reveals that long-term HD patients tend to have more periventricular abnormalities, which is significant when considering mild cognitive impairment as it can potentially lead to dementia. In particular, periventricular white matter hyperintensities related to cognitive impairment can be more detrimental than other types of mild cognitive impairment resulting from vascular damage.^{30,31}

According to our findings, there is a link between the length of HD and anomalies in key brain areas like the subcortex, white matter, corpus callosum, periventricular area, and global atrophy. Furthermore, Chen et al. discovered that decreased inter-hemispheric connection is directly related to cognitive impairment and corpus callosum atrophy, with the latter indirectly contributing to

cognitive impairment through its influence on inter-hemispheric connectivity.³²

Our research has revealed that there is a negative correlation between executive function and log-transformed white matter hyperintensity, indicating that both directly and indirectly impact the cognitive abilities of the patient. Furthermore, we observed a positive correlation between executive function and educational level.³³ Additionally, our results demonstrate a remarkable association between cognitive disorders and global brain atrophy.³⁴ The data suggests that the duration of HD can lead to microvascular disease, which may overlap with cognitive impairment, further underscoring the importance of regular cognitive assessments for individuals with long-term HD.

There are some limitations in our research that require additional investigation. Firstly, using an fMRI device to measure oxygen levels and blood flow could provide more precise outcomes. Due to the low imaging resolution, partial volume effects are unavoidable in our study; hence, a high-resolution imaging sequence must be used in future studies. Secondly, when analyzing brain activity, the physiological changes associated with aging, such as brain atrophy, must be considered.

Conclusions

Our study reveals that patients who have undergone long-term HD exhibit periventricular white matter disease in the subcortical region. Furthermore, this phenomenon tends to be more pronounced in elderly patients and those with lower levels of education, highlighting the need for age-specific and education-specific interventions.

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

Hemodialysis: HD; Chronic Kidney Disease: CKD; End-stage renal disease: ESRD; Magnetic Resonance Imaging: MRI; Computed tomography: CT; White matter disease: WMD; Mean Corpuscular Volume: MCV; Mean Corpuscular Hemoglobin: MCH; Mean Corpuscular Hemoglobin Concentration: MCHC; Red blood cell Distribution Width: RDW; Mean Platelets Volume: MPV; Platelet-Large Cell Ratio: P-LCR; Blood Urea Nitrogen: BUN; Periventricular Abnormality: PVAB; Subcortical Abnormality: SCAB; White Matter Disease: WMAB; Pons Abnormality: PAB; Global Brain Atrophy: GBAT; Thinning of Corpus Callosum: TCC; Frontal Lobe Atrophy: FLA; No Vessel Problem: NVP; Vessel Problem: VP.

Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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Role of the funding source

None.

Availability of data and materials

The data used in this study are available from the corresponding author on request.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. The authors of this study have adhered strictly to ethical issues (such as plagiarism and data fabrication, as well as double publication). Each subject signed a consent form before they were admitted to the study. Ethics approval was also received from Zahedan University of Medical Sciences and the ethics committee (IR.ZAUMS.REC.1395.361). Also, during the study, patients would be excluded from research if they did not consent to continue their research.

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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