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ORIGINAL: Brain Magnetic Resonance Imaging Findings in Chronic Kidney Disease Patients with and without Parkinsonism: A Case-Control Study

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ABSTRACT

Introduction: Chronic kidney disease (CKD) poses a major public health concern on a global scale. Patients with CKD have a heightened risk of developing multiple movement disorders like parkinsonism. Timely diagnosis through imaging and effective management may hold the key to mitigating disease symptoms.

Material and Methods: Twenty-eight individuals with CKD were categorized into two groups, nine patients showing signs of parkinsonism and a control group of nineteen patients without parkinsonism. All participants underwent non-contrast brain magnetic resonance imaging (MRI) scans, including T1, T2, DWI, and FLAIR sequences. The data were statistically analyzed using SPSS-24 and STATA software.

Results: Nine patients exhibited parkinsonism symptoms, while nineteen did not. Brain MRI revealed hypointensities in structures like the putamen, globus pallidus, and cerebellar dentate nucleus in both groups. Comparative analysis showed no statistically significant differences in the percentages of these findings ($P>0.05$). Similarly, the presence of cerebral atrophy and cerebrovascular disease did not significantly differ between the groups. Factors such as diabetes, hypertension, and history of dialysis also failed to show significant distinctions ($P>0.05$ for all).

Conclusion: The correlation between brain MRI alterations in CKD patients with parkinsonism symptoms and those without was not significant. Nevertheless, there was a strong association between the duration of CKD in patients and the presence of parkinsonism-related signs.

Introduction

Chronic kidney disease (CKD) represents a significant global public health challenge, affecting more than 10% of the world's population and over 50% of adults aged 70 and above (1). Uremia resulting from chronic kidney failure impacts various body systems, giving rise to multiple signs and symptoms (2). The severity of these manifestations is influenced by the progression of the disorder, comorbid

conditions, and the patient's age. Among CKD patients' the most prevalent neurological manifestations are impaired consciousness, diminished concentration and cognition, orientation disturbances, restless legs, burning sensations in the soles of the feet, muscle spasms, stroke and convulsions (3-6). While the underlying mechanisms responsible for most of these manifestations are being investigated, it is postulated that the accumulation of uremic waste materials has a neurotoxic effect that may contribute to these signs and symptoms (7, 8).

Parkinsonism is a neurological complication observed in patients with chronic kidney failure. This association is investigated by many studies (9-11). Neuroimaging findings in CKD patients have revealed bilateral symmetrical changes in the basal ganglia, suggesting the potential involvement of metabolic and vascular factors in developing such lesions (12).

Recent studies have drawn attention to the elevated prevalence of parkinsonism among individuals with kidney disease. A study showed uremic patients face a 1.81-fold higher risk of developing parkinsonism than the general population. In contrast, the risk of parkinsonism in end-stage renal disease (ESRD) patients after three years is 1.55 times higher than that of the comparison group (13).

Given the complications experienced by patients with renal failure, including neurological issues, and the potential benefits of faster diagnosis and early initiation of dialysis in individuals with chronic kidney failure, we sought to compare brain MRI findings between CKD patients presenting parkinsonism and those without such. Timely intervention and patient outcomes enhancement can be provided by initiating treatment before signs and symptoms appearance.

Methods

The present study employs a case-control design and focuses on patients diagnosed with chronic kidney failure. Individuals with IIIb, IV, and V CKD grades were included as the research population. Following a thorough assessment of the inclusion and exclusion criteria, patients underwent a comprehensive neurological examination conducted by qualified neurologists to identify any signs or symptoms of parkinsonism.

We conducted the present study in accordance with the relevant guidelines and regulations. According to the MDS Clinical Diagnostic Criteria for Parkinson's disease, patients were identified based on specific criteria. These criteria included primary motor manifestations used to diagnose Parkinson's disease. These criteria include bradykinesia, accompanied by either rest tremor, rigidity, or both (14).

Patients underwent brain magnetic resonance imaging (MRI) scans without contrast using a Siemens 1.5 Tesla device with T1, T2, FLAIR, and DWI sequences. The imaging results were subsequently evaluated and reported by a neurologist and a radiologist. Brain MRI scans were analyzed in two groups: patients presenting with parkinsonism symptoms and those without such symptoms. The objective was to assess the presence or absence of brain lesions and their location and characteristics to determine any disparities between the two groups and establish the significance of their relationship.

The study had specific requirements for selecting participants. Patients aged between 18 and 85 years with IIIb, IV, and V CKD grades were eligible. On the other hand, certain conditions led to exclusion from the study. These included: 1) having a positive family history of parkinsonism, 2) having brain lesions unrelated to kidney failure (e.g., large vessel lesions or space-occupying lesions) as observed in the patient's MRI, 3) experiencing persistent electrolyte imbalances that could cause parkinsonism (e.g., sodium levels below 120 ml eq/dl or above 160 ml eq/dl, calcium levels below 7 ml eq/dl), 4) showing signs of parkinsonism before being diagnosed with kidney failure, and 5) developing parkinsonism symptoms after using drugs known to induce such

symptoms (e.g., neuroleptic drugs, tetrabenazine, lithium).

Nineteen CKD patients were selected, referred to the clinic, and compared to nine CKD patients with parkinsonism to determine the required study participants. The patients were divided into two groups: the first group consisted of CKD patients with parkinsonism, while the second group comprised CKD patients without. The allocation of patients to the second group was determined using a simple block randomized round method with computer-generated numbers. This process ensured that the inclusion and exclusion criteria were correctly followed.

Statistical analysis

Data obtained from the study underwent rigorous quality control measures and a final review before being subjected to statistical analysis. SPSS24 (IBM, Armonk, NY, USA) and STATA (StataCorp LLC, Texas, USA) software were utilized, along with chi-square tests, to perform the analysis. Given that the response variable, namely the presence or absence of changes in MRI, was binary (yes or no), logistic regression analysis was employed to investigate the association between age, renal failure, diabetes status, and gender variables with changes in MRI within the two patient groups. We considered P-values of less than 0.05 statistically significant.

Results

The current study investigated changes in cerebral MRI scans in patients suffering from chronic renal failure who showed parkinsonism symptoms. Initially, 165 patients diagnosed with chronic renal failure (graded IIIb, IV, and V) were considered for inclusion. Among them, 15 patients displayed parkinsonism symptoms. However, four individuals did not meet the inclusion criteria, and two patients did not cooperate during the study, so they were excluded. As a result, a control group of 19 individuals without parkinsonism symptoms was included, carefully matched with the patient group regarding age and gender. Ultimately, the study comprised 28 patients with chronic renal failure, including nine with parkinsonism symptoms and 19 without (as the control group). Among the control group, 14 (50%) were female, and 14 (50%) were male.

Five male patients (36%) were assigned to the parkinsonism group, while nine (64%) were placed in the control group. Among the female participants, four individuals (28%) were in parkinsonism, while ten individuals (72%) were in the control group.

The results of the t-test (P>0.05) concluded that there is no significant association between the presence of parkinsonism and the patient's BMI, sodium levels, creatinine levels, and calcium levels (***Table 1***).

The mean duration of CKD in the group exhibiting parkinsonism symptoms was 53.56 months. In contrast, 36.63 months in the group without parkinsonism symptoms (P=0.06), indicating a lack of statistical significance.

Table 1. BMI, sodium (Na), creatinine (Cr), and calcium (Ca) levels among parkinsonism and non-parkinsonism groups

Variable	Parkinsonism (n=9) Mean ± SD	Non-parkinsonism (n=19) Mean ± SD	P-value
BMI	29.88 ± 5.10	27.92 ± 3.12	0.096
Na (mEq/dL)	135.17 ± 5.31	138.23 ± 4.60	0.606
Cr (mg/dL)	3.16 ± 1.19	3.05 ± 1.51	0.168
Ca (mg/dL)	8.38 ± 0.79	8.63 ± 0.77	0.877

The analysis, conducted using the Yeoman-Whitney test, revealed a significant positive correlation between the presence of parkinsonism symptoms and the duration of CKD in patients. Moreover, there is a discernible difference between the presence of parkinsonism and the duration of CKD in the patient population.

The relationship between parkinsonism and diabetes, hypertension, and CKD III, IV, and V grades was evaluated using the chi-square test. The findings indicate no significant relationship exists between parkinsonism and mentioned factors in patients (***Table 2***).

Also, there was no significant relationship between the presence of parkinsonism and the patient's history of dialysis.

The relationship between parkinsonism and putamen hypointensity, globus pallidus hypointensity, cerebellar dentate nucleus hypointensity, cerebral atrophy, and cerebral small vessel disease in brain MRI was explored. The analysis, conducted using the non-parametric Chi-square test (P>0.05), indicates no significant correlation between the presence of parkinsonism symptoms and all of the above parameters in the brain MRI of the patients (***Table 3***).

Table 2. Diabetes, hypertension, and CKD grades in patients with and without parkinsonism

Variables	Groups	N (%)	P-value
Diabetes	Parkinsonism (n=9)	5 (55.6)	0.06
	Non-Parkinsonism (n=19)	11 (57.9)	
Hypertension	Parkinsonism (n=9)	4 (44.4)	0.689
	Non-Parkinsonism (n=19)	11 (57.9)	
CKD Grade III	Parkinsonism (n=9)	3 (33.3)	0.291
	Non-Parkinsonism (n=19)	11 (57.9)	
CKD Grade IV	Parkinsonism (n=9)	2 (22.2)	
	Non-Parkinsonism (n=19)	1 (5.3)	
CKD Grade V	Parkinsonism (n=9)	4 (44.4)	
	Non-Parkinsonism (n=19)	7 (36.8)	

Table 3. Brain MRI changes in CKD patients and association with parkinsonism

Brain MRI findings	Groups	N (%)	P-value
Putamen hypointensity	Parkinsonism (n=9)	6 (66.7)	0.139
	Non-Parkinsonism (n=19)	7 (36.8)	
Globus pallidus hypointensity	Parkinsonism (n=9)	5 (55.6)	0.35
	Non-Parkinsonism (n=19)	7 (36.8)	
Cerebellar dentate nucleus hypointensity	Parkinsonism (n=9)	1 (11.1)	0.575
	Non-Parkinsonism (n=19)	1 (5.3)	
Cerebral atrophy	Parkinsonism (n=9)	6 (66.7)	0.339
	Non-Parkinsonism (n=19)	9 (47.4)	
Cerebral small vessel disease	Parkinsonism (n=9)	8 (88.9)	0.963
	Non-Parkinsonism (n=19)	17 (89.5)	

Discussion

Uremia resulting from chronic kidney failure affects multiple body systems and increases the risk of developing dementia, particularly in individuals with vascular risk factors (15). Neurological manifestations commonly observed in these patients include impaired consciousness, reduced concentration, orientation disorder, restless legs, burning soles, muscle spasms, and seizures (16, 17). Parkinsonism is among the neurological disorders prevalent in patients with chronic kidney failure. Studies have demonstrated that uremic patients have a 1.81 times higher risk of developing Parkinson's disease than the general population, significantly increasing after three years of CKD (13).

In a study by Yao et al. in 2021, progressive CKD patients experienced a greater prevalence and severity of cerebral small vessel disease linked to a decline in renal function (18). In another study, Chang and colleagues found that impaired kidney function was associated with reduced cortical thickness and small cerebral gray matter volume (19). We conducted a case-control study investigating brain MRI changes in chronic renal failure patients with parkinsonism symptoms. Brain MRI analyses in our study revealed putamen and globus pallidus hypointensity in the T2 view and hyperintensity in the T1 view. It also showed cerebellar dentate nucleus hypointensity, brain atrophy, and small vessel disease. However, the CKD group without parkinsonism symptoms exhibited a higher incidence of these changes. No statistically significant difference was observed between the two groups. Additionally, a meaningful relationship was found between the duration of CKD and the occurrence of parkinsonism, indicating that a more extended period of

CKD increases the likelihood of developing parkinsonism.

Wang et al. examined 12 patients with a history of CKD and diabetes mellitus who presented with acute-onset parkinsonism and dyskinesia symptoms, and neuroimaging findings revealed bilateral symmetrical changes in the basal ganglia. These changes improved during the treatment of clinical signs and regressed in subsequent radiological examinations (12). The results of this study show that CKD patients are susceptible to basal ganglia changes and the development of parkinsonism, which was consistent with our research findings. Although the incidence of MRI changes in the basal ganglia was higher in patients with parkinsonism symptoms compared to the control group in our study, this difference was not statistically significant.

In a case report by Lee et al., a 48-year-old male patient with advanced renal failure presented with parkinsonism symptoms such as balance and gait disturbances. MRI imaging revealed bilateral basal ganglia lesions, further confirmed through DWI, SPECT, and MRA examinations, which indicated vasogenic edema secondary to slight vessel dilation (20). These findings support the theory that parkinsonism symptoms in CKD patients can be attributed to basal ganglia changes, possibly involving the mechanism of vasogenic edema.

A case series review conducted by Manickavasagar et al. in 2022 examined patients undergoing dialysis who presented with acute parkinsonism. The study discovered the existence of clinical extrapyramidal movement disorders, which were identified using specific diagnostic MRI imaging (21). These findings support diagnosing extrapyramidal syndromes related to CKD and dialysis.

Osaki et al. reported a 71-year-old male patient with a history of diabetes, hypertension, and ESRD undergoing hemodialysis who presented with post-dialysis organ failure. The patient exhibited akinesia, rigidity without tremors, weakness in the proximal limbs, increased deep tendon reflexes, and a positive Babinski sign. MRI imaging revealed a hyperintense lesion in the lentiform nucleus in the T2 view. Following treatment with levodopa and steroids, hyperintense lesions decreased in the T2 view (22). This case report demonstrated that ESRD patients might experience parkinsonism symptoms associated with basal ganglia changes, consistent with our study. The differences in MRI findings compared to our study may be attributed to the patients' sample variations, with the examined patient presenting with acute symptoms.

In another study by Kim et al., 10 patients with uremic encephalopathy were investigated, nine of whom had a history of chronic kidney disease, while one had acute kidney failure. T2 imaging brain MRI studies revealed hyperintense lesions in the basal ganglia, known as the lentiform fork sign, with varying degrees of diffusion restriction in diffusion-weighted imaging sequences. Complete resolution of the lesions was observed in four patients following hemodialysis (23). While our study revealed a significant correlation between the duration of CKD and the occurrence of parkinsonism, Kim et al.'s study did not include the duration of renal disease as a contributing factor.

Yoon et al.'s study focused on two uremic encephalopathy patients presenting with parkinsonism symptoms, paroxysmal head dystonia, and acute lower limb mono paresis, accompanied by unusual radiological manifestations. Brain MRI revealed abnormalities in the basal ganglia and cortex and hemorrhagic infarcts in the internal capsule. Bilateral symmetric basal ganglia lesions were observed, hyperintense in the T2 view and hypointense in the T1 view, and clinical symptoms improved after hemodialysis (24). Our and this study showed that uremic patients might experience parkinsonism symptoms associated with basal ganglia changes. However, the MRI changes in basal ganglia signal intensity differed from our study, likely due to differences in the studied patient population. Our study focused on CKD patients, while the two recent studies examined patients with uremic encephalopathy.

To talk about limitations, this study had a relatively small sample size which may reduce the statistical power of the analysis. It also did not address potential confounding factors influencing the relationship between CKD and parkinsonism, such as medication use, comorbidities, or lifestyle factors. Also, selecting patients from a specific nephrology clinic may introduce selection bias.
Regular screenings are recommended for parkinsonism in CKD patients. Raising awareness among medical professionals, conducting systematic reviews, investigating the pathophysiology of risk factors, and performing larger-scale studies to validate findings are crucial. Considering the high occurrence of parkinsonism in CKD patients and the risk of early-onset dementia, patients with CKD stages III, IV, and V should undergo regular neurological evaluations, including brain MRI if necessary. Nephrologists should prioritize assessing parkinsonism symptoms and make appropriate referrals to neurologists when required. Future studies should address the limitations by designing prospective studies using available information and robust statistical methods for more comprehensive and reliable results.

Conclusion

Our study discovered that CKD patients with parkinsonism displayed brain MRI changes but did not reach statistical significance. No substantial variations were observed in the demographic or clinical features between the two groups and duration of having CKD was significantly associated with parkinsonism signs.

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Ethical standards statement

The protocol of this study was approved by the Research Ethics Committee of Mazandaran, University of Medical Sciences (code: IR.MAZUMS.REC.1398.815). All patients voluntarily participated and provided informed consent by completing the necessary consent form.

Conflicts of interest

The authors declare no conflict of interest.

Authors' contributions

Sedigheh Varyani and Hamed Cheraghmakani designed the main idea of the research. Sedigheh Varyani and Alireza Karimi Varaki collected patients' data and statistical analysis. Mehran Frouzanian contributed by writing the main manuscript and suggesting improvements to the research and creating tables. Seyed Mohammad Baghbanian contributed to statistical analysis and suggestions for the discussion part of the manuscript. Atieh Makhlough contributed to the nephrology segments of the research and suggestions for discussion. Rohollah Abdi contributed and collaborated with the radiologic segments of the research and MRI findings. All authors reviewed the manuscript.

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