



Dialysis headache: prevalence and clinical presentation in hemodialysis and kidney transplant patients

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Abstract

Introduction

Headache is a common symptom among hemodialysis patients, with a prevalence around 70%. Dialysis headache is defined according to International Classification of Headache Disorders (ICHD-3) as a headache without specific characteristics, occurring during and caused by hemodialysis that spontaneously disappears within 72 hours after the dialysis session. There is no consensus on trigger factors or physiopathology.

Objective

To evaluate prevalence, clinical characteristics, and associated factors with dialysis headache.

Methods

Observational study with quantitative analysis. Study patients were divided into two groups: (1) 25 hemodialysis patients(HD) and (2) 25 early post kidney transplant patients(Tx). A structured questionnaire was applied to all patients, including Hospital Anxiety and Depression Scale (HADS) and Epworth Sleepiness Scale. Laboratory data, blood pressure and body weight were analyzed before and after one dialysis session.

Results

In group HD, eight patients (32%) had diagnosis of dialysis headache, with pulsating headache (n=6, 75%), photophobia (n=6, 75%), phonophobia (n=4, 50%), and nausea or vomiting (n=6, 75%), with a pain score of 7.75 ± 1.58 . Headache group had higher scores of anxieties (7.00 ± 3.93 vs. 3.82 ± 3.23 , $p=0.03$) and sleepiness (9.13 ± 3.94 vs. 4.76 ± 3.85 , $p=0.01$), lower levels of serum calcium ($p=0.01$), and higher systolic ($p=0.02$) and diastolic ($p=0.02$) blood pressure pre-dialysis. In group Tx, five patients (20%) reported dialysis headache, with pulsating headache (n=4, 80%), nausea or vomiting (n=4, 80%), with a pain score of 8.0 ± 1.41 . Headache group had a higher score of sleepiness (9.20 ± 4.32 vs. 4.80 ± 4.51 , $p=0.029$) and were younger (38.93 ± 14.43 vs. 54.02 ± 8.31 years of age, $p=0.03$).

Conclusion

Headache is frequent among hemodialysis patients and had similar symptoms of migraine. In this series dialysis headache was associated with higher scores of anxieties and sleepiness, higher blood pressure and lower calcium pre dialysis.

Keywords:
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Introduction

Hemodialysis is one alternative therapy to chronic kidney disease (CKD). Headache is frequent among dialysis patients, with a prevalence ranging from 27% to 70% in different series.^{1,2} The frequency of headache in patients with CKD in stages 3 and 4 is comparable to general population¹ but increases with initiation of dialysis therapy, with a higher frequency in hemodialysis compared to peritoneal dialysis³ suggesting that hemodialysis per se is a risk factor, instead of metabolic alterations of CKD. However, physiopathology remains controversial and there is a lack of large studies in this population.

Dialysis headache was first described in 1972 by Bana et al.⁴, who proposed that headache was secondary to water and electrolyte exchange during dialysis. However, other studies advocated different mechanisms for this disease that varies according to dialysis characteristics, environmental factors, and individual background.

The 2nd edition of the International Classification of Headache Disorders (ICHD-2) defined headache attributed to dialysis as a headache occurring during hemodialysis that disappears within 72 hours post dialysis and emerges in at least half of hemodialysis sessions to make a total of at least three attacks. In the 3rd edition, ICHD-35, headache dialysis is described as a headache without specific characteristics, that occurs during dialysis, triggered by dialysis and spontaneously disappear within 72 hours after the end of dialysis session. Diagnostic criteria include patients on dialysis with at least three episodes of acute headache fulfilling one of the following criteria: (a) each headache attack was developed during a dialysis session; (b) each episode was worsened during dialysis session and/or each headache attack was resolved within 72 hours after the end of dialysis session; (c) headache episodes cease altogether after a successful kidney transplant and termination of dialysis, and (d) headache was not better accounted by another ICHD-3 diagnosis.⁵

There is no consensus on physiopathology or trigger factors for dialysis headache. Different studies suggest a series of possible factors, such as biochemical changes, especially in urea, sodium, and magnesium; blood pressure variations during dialysis session; pre-dialysis hypotension; plasmatic renin and aldosterone reduction; fluctuations in calcitonin gene related peptide (CGRP) levels and substance P.^{1,2} One hypothesis considers a rapid reduction in serum urea levels after dialysis, not followed by a similar reduction in urea concentration in the brain. Higher brain urea during dialysis causes a transient increase in intracranial pressure,

with brain edema and headache, with a disequilibrium syndrome, explaining the headache beginning after dialysis and persisting until intracranial pressure normalizes.¹ Depression, anxiety and other sleep disorders are also involved in dialysis headache pathology.¹

The aim of this study was to evaluate the prevalence, clinical presentation, and associated factors of dialysis headache, in order to identify strategies to prevent and treat this disorder and improve the quality of life of dialysis patients.

Methods

Chronic kidney disease patients, older than 18 years old, receiving renal replacement therapy by hemodialysis from December 2021 and May 2022, were included in this observational study with quantitative analysis. Exclusion criteria were cognitive impairment or the patient incapable of answering the structured questionnaire. Study protocol was approved by the local Ethics Committee (CAAE-53039821.8.0000.5404). All included patients signed the informed consent and were divided into two groups: (HD) 25 patients on hemodialysis and (Tx) 25 patients in early post-kidney transplant treated by hemodialysis while on a waiting list. This study was conducted at the Nephrology Division of Clinics Hospital, University of Campinas, São Paulo, Brazil.

Included patients were interviewed by one of the researchers, using a structured questionnaire that includes demographic data, headache characteristics and comorbidities. Dialysis headache was diagnosed according to 3rd edition of the International Classification of Headache Disorders (ICHD-3).⁵ Humor and sleep disorders were evaluated by Hospital Anxiety and Depression Scale (HADS)⁶, and Epworth Sleepiness Scale⁷, both translated and validated for the Portuguese language.

Hemodialysis patients were interviewed in the first (initial) and last (final) dialysis sessions in a week. Hemodialysis regimen included three sessions of hemodialysis in a week, every two days, with a duration of 3h30 to 4h, adjusted according to body weight and remaining diuresis of patients. Dialysis headache was evaluated in a retrospective questionnaire at initial visit and in a prospective manner at the end of dialysis sessions, comparing the first and last day in the week. These



two points were fixed to reduce the chance of bias associated with changes in body dry weight among dialysis sessions. During initial interview, a neurological exam was also performed. Blood pressure was measured by manual sphygmomanometer and body weight by a digital body scale, before and after every dialysis session. Blood samples were collected at beginning and end of the first session of the week and analyzed for urea, glucose, sodium, potassium, calcium, and magnesium concentrations. Hemodialysis patients without headache symptoms were considered as controls.

Transplant patients were interviewed from five to seven days after a kidney transplant, considering this period for normalization of graft renal function and patients free of posttransplant dialysis. Headache was evaluated by a retrospective questionnaire, considering pre transplant dialysis therapy. Humor and sleep disorders were also analyzed in this group. Patients without antecedents of headache were considered as transplant control group.

Statistical analysis was performed by real statistics for excel. Numerical data was expressed as mean and standard deviation and analyzed by Student t-test or Mann-Whitney test. Categorical data were expressed as percent of data and analyzed by chi-square. Results were considered statistically significant if $p < 0.05$.

Results

Fifty patients fulfilled the inclusion criteria, 25 in the HD group and 25 in the transplant (Tx) group. In the retrospective interview of HD group, eight (32%) reported headache that could be classified as dialysis headache according to ICHD-3 criteria. Five patients (63%) reported headache previously to hemodialysis therapy and three (37%) developed headache after the beginning of renal replacement therapy. Headache characteristics included pulsating headache ($n=6$, 75%), photophobia ($n=6$, 75%), phonophobia ($n=4$, 50%), nausea and vomiting ($n=6$, 75%) with a mean analogical pain score of 7.75 ± 1.58 .

In the prospective analysis of 23 HD patients, comparing dialysis session for one week, three (13%) reported headache in the first session of the week and five (21.7%) in the last session. There were no reports of headache within the dialysis sessions during the observational week (Table 1).

Table 1. Age distribution of the 115 medical residents who participated in the study

	Global	Headache	Control	p
Patients	25	8	17	
Sex (male)	13 (52%)	3 (38%)	10 (59%)	0.32
Age (years)	39.7 ± 14.8	39.9 ± 12.9	41.0 ± 16.2	0.71
Body mass index (Kg/m²)	22.2 ± 3.3	21.7 ± 2.9	22.5 ± 3.6	0.61
Dialysis lenght (months)	56.2 ± 67.0	61.75 ± 53.6	53.6 ± 67.0	0.51
Anxiety score	4.84 ± 3.63	7.0 ± 3.93	3.82 ± 3.23	0.02
Depression score	3.96 ± 3.56	4.50 ± 3.96	3.71 ± 3.57	0.62
Sleepiness (Epworth)	6.16 ± 4.24	9.13 ± 3.94	4.76 ± 3.85	0.01

Anxiety and depression score- HADS questionnaire.

Patients with headache dialysis had higher anxiety (7.00 ± 3.93 vs. 3.82 ± 3.23 , $p=0.03$), and sleepiness scores (9.13 ± 3.94 vs. 4.76 ± 3.85 , $p=0.01$), compared to control hemodialysis patients. Lower serum calcium (7.87 ± 0.74 mEq/L vs. 8.93 ± 0.64 mEq/L, $p=0.01$) and higher systolic (160.0 ± 10.0 mmHg vs. 134.5 ± 17.0 mmHg, $p=0.01$) and diastolic (100.0 ± 10.0 mmHg vs. 82.5 ± 9.1 mmHg, $p=0.02$) levels at beginning of dialysis occurred in the headache group compared to controls (Table 2).

Table 2. Laboratory parameters among hemodialysis patients

		Headache	Control	p
Urea (mg/dl)	Pre dialysis	119.0 ± 10.5	132.2 ± 43.9	0.61
	Post dialysis	31.0 ± 14.1	36.4 ± 15.7	0.58
	Δ pre-post	88.0 ± 4.36	95.8 ± 36.9	0.72
Urea reduction rate	Urea pos/urea pre	0.75 ± 0.1	0.71 ± 0.12	0.89
Sodium (mEq/L)	Pre dialysis	138.3 ± 2.5	137.3 ± 2.8	0.58
	Post dialysis	138.0 ± 4.6	136.2 ± 2.44	0.29
	Δ pre-post	0.33 ± 3.7	0.45 ± 2.42	0.94
Potassium (mEq/L)	Pre dialysis	4.8 ± 0.2	5.1 ± 1.1	0.43
	Post dialysis	3.4 ± 0.35	3.4 ± 0.5	0.79
	Δ pre-post	1.5 ± 0.3	1.2 ± 0.4	0.97
Calcium (mEq/L)	Pre dialysis	7.87 ± 0.74	8.93 ± 0.64	0.01
	Post dialysis	9.20 ± 0.6	10.08 ± 1.08	0.19
	Δ pre-post	-1.33 ± 1.31	-0.69 ± 1.49	0.48
Magnesium (mEq/L)	Pre dialysis	1.98 ± 0.41	1.88 ± 0.31	0.63
	Post dialysis	1.61 ± 0.19	1.61 ± 0.12	0.98
	Δ pre-post	0.37 ± 0.25	0.24 ± 0.29	0.46
Glucose (mg/dl)	Pre dialysis	82.3 ± 13.6	96.4 ± 29.4	0.43
	Post dialysis	73.7 ± 14.5	109.4 ± 41.6	0.16
	Δ pre-post	8.6 ± 10.2	-10.0 ± 39.1	0.42
Osmolarity 2(Na+K)+(glu/18)+(U/6)	Pre dialysis	310.8 ± 3.03	312.2 ± 11.1	0.82
	Post dialysis	291.9 ± 7.22	291.4 ± 7.8	0.91
	Δ pre-post	18.8 ± 6.9	20.8 ± 8.2	0.68
Body weight (Kg)	Pre dialysis	59.10 ± 15.16	60.92 ± 13.11	0.83
	Post dialysis	57.23 ± 15.03	58.82 ± 13.02	0.85
	Δ pre-post	1.87 ± 1.07	2.10 ± 1.14	0.75
Systolic BP (mmHg)	Pre dialysis	160.0 ± 10.0	134.5 ± 17.01	0.02
	Post dialysis	150.0 ± 17.32	122.5 ± 21.97	0.06
	Δ pre-post	10.0 ± 10.0	12.0 ± 16.42	0.84
Diastolic BP (mmHg)	Pre dialysis	100.0 ± 10.0	82.5 ± 9.1	0.018
	Post dialysis	93.3 ± 11.5	78.0 ± 11.5	0.08
	Δ pre-post	6.7 ± 5.8	4.5 ± 13.2	0.57



In the posttransplant group, five patients (20%) reported dialysis headache according to ICHD-3. In four patients, headache started after the beginning of renal replacement therapy. Headache history was of pulsating headache (n=4, 80%), nausea and vomiting (n=4, 80%), worsening after physical activity (n=3, 60%) with a mean analogical pain score of 8.00 ± 1.41 . Transplant patients who reported previous dialysis headache were younger (38.9 ± 14.4 years vs. 54.0 ± 8.3 years, $p=0.03$), and had a higher sleepiness score (9.20 ± 4.32 vs. 4.80 ± 4.51 , $p=0.03$) than transplant controls (Table 3).

Table 3. Demographic data and comorbidities among transplant patients

	Global	Headache	Control	P
Patients	25	5	20	
Sex (male)	14 (56%)	2 (40%)	12 (60%)	0.42
Age (years)	51.0 ± 11.1	38.9 ± 14.4	54.0 ± 8.3	0.03
Body mass index (Kg/m²)	26.0 ± 4.2	24.4 ± 5.0	26.4 ± 4.2	0.40
Dialysis length (months)	29.5 ± 25.9	33.2 ± 16.0	28.6 ± 28.8	0.30
Anxiety score (HADS)	5.0 ± 4.39	5.40 ± 4.51	4.90 ± 4.59	0.86
Depression score (HADS)	2.88 ± 3.37	3.80 ± 4.76	2.65 ± 3.15	0.67
Sleepiness (Epworth)	5.68 ± 4.65	9.20 ± 4.32	4.80 ± 4.51	0.03

Discussion

In this study we observed a prevalence of dialysis headache of 32% in hemodialysis patients and 20% in renal transplant recipients. Previous studies report a prevalence ranging from 6.6% to 70%.^{1,2} These disparities can be attributed to the criteria applied for dialysis headache classification, as few studies are based on ICHD-3 criteria.

The ICHD-35 defines dialysis headache as a headache that occurs during dialysis, is caused by dialysis and spontaneously disappear within 72 hours after the end of dialysis session. Difference in criteria between second and third International Classification of Headache Disorders is important and can impact in dialysis headache diagnosis.⁸ Recent studies with ICHD-3 suggests a prevalence of 35.4% to 49%.⁸⁻¹⁰

This study perceived a heterogeneity in dialysis headache, with symptoms like migraine. Majority of patients reported moderate to intense pain, pulsating headache, associated with photophobia, phonophobia, nausea and vomiting. Headache was bilateral, frontal, or parietal, and sometimes holocranial, similar to previous reports of dialysis headache.^{8,11}

Humor and sleep disorders can be associated with

dialysis headache, acting as trigger factors. In this series we observed higher scores of anxiety and sleepiness in patients with headache during hemodialysis therapy and higher sleepiness scores in patients submitted to kidney transplant who reported dialysis headache.

Sleep disturbances can modulate the headache presentation, acting as a trigger factor, or exacerbating a preexisting headache. However, in some primary headaches, sleep can reduce symptoms, with a bimodal influence.^{12,13} Likewise, secondary headaches can be modulated by sleep disorders. Length and quality of sleep can induce dialysis headache. Hemodialysis patients sometimes modify their sleep pattern to reduce post-dialysis symptoms, such as fatigue, metabolic alkalosis or hypotension. However, these changes can also induce or aggravate preexisting sleeping disturbances.

Humor disorders, mainly anxiety and depression, are frequently associated with headache in different population based studies, and have an increased prevalence among CKD patients on renal replacement therapy.¹⁴ Previous reports showed a prevalence of anxiety symptoms of 19% (IC 95%: 11-27%) in patients with CKD, and symptoms of higher anxiety of 43% (IC 95%: 36-50%).¹⁵ Among hemodialysis patients the prevalence of anxiety ranges from 12% a 52%.¹⁶ We should consider that patients with anxiety are prone to have dialysis headache and that dialysis headache can exacerbate anxiety symptoms, generating a vicious circle.

In this series we did not observed an association of headache and depression, quantified by HADS score. However, a recent study, using the depression scale PHQ-9 observed an association between dialysis headache and mild depression.⁹ The absence of association in our series can be secondary to a small sample or the accuracy of the depression score questionnaire.

Hemodialysis patients with headache had lower serum calcium levels pre-dialysis. Calcium receptors and calcium channels have been associated to pain mechanism.¹⁷ Genetic studies showed an association of migraine with calcium levels and calcium channels PQ voltage dependent, suggesting the participation of calcium in pathophysiology of some types of headache.¹⁸ Hypercalcemia has been associated with chronic pain in dialysis patients, including headache muscle and neural pain¹⁹, suggesting that changes in serum calcium levels can modulate beginning and maintenance of dialysis headache.



The ICHD-3 suggests that urea, sodium and magnesium levels can be risk factors for dialysis headache⁵, as well as subtle reduction in urea levels or variation in blood osmolarity.^{8,9,11} In this series, analysis of metabolic parameters pre- and post-dialysis did not show significant changes, in control patients or in dialysis headache group. Blood pressure variations are considered a risk factor for dialysis headache according to ICHD-3.⁵ Changes in blood pressure during dialysis are frequent and have been considered as a trigger factor for headache.^{8,9,11} Hypotension can be associated to vasodilation of brain vessels, with a mechanism similar to headache associated to anti-hypertensive drugs such as hydralazine or calcium channel blockers.¹¹ In the present series we observed higher pre-dialysis blood pressure, systolic and diastolic, in headache group. However, symptoms of these patients did not fulfill criteria to be considered as a hypertensive encephalopathy.

Dialysis headache therapy remains controversial as the etiology is not clear and due to a lack of clinical trials or large series of cases. The multifactorial etiology implicates an individualized approach, and therapeutical arsenal includes amitriptyline, angiotensin converting inhibitors, chlorpromazine, magnesium supplements, botulin type A toxin and frequent dialysis.¹ Likewise, treatment of humor and sleep disorders have a positive impact in controlling dialysis headache. In our series, alongside of anxiety and sleepiness disorders, other possible targets for therapy were blood pressure and calcium pre-dialysis.

Limitations of this study are the small number of patients in dialysis and a single center. We should consider that blood pressure was documented from routine dialysis files, and variances in measurement according to professional and equipment cannot be ruled out. As patients also receive a snack during dialysis session, usually with tea or coffee and bread or cookies, the association between dialysis headache and caffeine and glucose could not be assessed.

Conclusion

Dialysis headache is frequent among hemodialysis patients, have a clinical presentation like migraine and is associated with anxiety, sleepiness and pre-dialysis hypocalcemia and hypertension. Treatment of these risk factors can attenuate the incidence of dialysis headache, resulting in a better quality of life in hemodialysis.

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Conflict of interest

Authors have no conflict of interest to declare.

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Authors' contribution

All the authors had the same contribution.

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