ORIGINAL ARTICLE

Hemodialysis-related headache and how to prevent it

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Background and purpose: Hemodialysis (HD) may have some adverse effects on the nervous system. Headache is the most commonly reported neurological symptom amongst HD patients. Our aim was to determine the frequency, clinical characteristics and triggering factors of HD-related headache (HRH) and to evaluate preventive strategies for reducing HRH.

Method: In all, 494 patients were included. Comparative controls (CC) were classified within the same patients without headache. Arterial systolic/diastolic blood pressure, blood urea nitrogen (BUN) and creatinine were correlated before/after one HD. The urea reduction ratio during the dialysis session was determined.

Results: A total of 175 patients (35.4%) with a mean age of 57.3 ± 15.7 years were diagnosed with HRH. HRH was more common in males ($P < 0.001$). Headache was started a mean of 2.90 ± 0.86 h after the HD. The common localization of pain was reported to be bifrontal in 41.7% ($n = 73$). The mean duration of headache was 6.22 ± 7.8 h, with a duration of ≤4 h reported by 64.0% of patients. The mean Visual Analog Scale score was 5.64 ± 2.05. The differences between pre/post-dialysis BUN values were 94.6 ± 31.1 in HRH patients and 86.8 ± 28.5 in the CC group ($P = 0.006$). The systolic blood pressure difference between the pre/post-dialysis measurements was 22.4 ± 16.5 mmHg in HRH patients and 12.8 ± 19.4 mmHg in CC ($P < 0.001$). Patients with HRH had significantly higher mean systolic and diastolic blood pressure pre-dialysis values (systolic, $P = 0.002$; diastolic, $P < 0.001$). The differences in systolic/diastolic blood pressure between pre/post-dialysis were higher in the HRH group ($P < 0.001$, $P = 0.001$, respectively).

Conclusion: Regulating the frequency and timing of dialysis may provide better management in HRH with high BUN levels and high pre-dialysis blood pressure.

Introduction

Neurological complications of uremic encephalopathy are thought to be mediated by impaired neurotransmission [1] and constitute an important cause of morbidity and mortality in patients with chronic renal failure. Hemodialysis (HD) increases the life expectancy of these patients by decreasing systemic and neurological complications. However, the dialysis may in itself have deleterious effects on the nervous system. Dialysis dementia, dialysis disequilibrium syndrome, hypertensive encephalopathy and stroke can occur either directly or indirectly in relation to HD [2,3].

Headache is one of the most commonly reported neurological symptoms amongst HD patients [4,5]. Three types of headache can occur in these patients

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[6]: (i) headache with onset during dialysis, without headache antecedents and fulfilling the criteria for headache related to HD (HRH) based on the International Classification of Headache Disorders 2nd edn (ICHD-II) classification; (ii) headache that worsens during dialysis sessions with antecedents of primary headaches; (iii) headache with onset during dialysis without headache antecedents but with headache occurring between the sessions >50% of the time and therefore not fulfilling the criteria for HRH based on ICHD-II classification. According to the International Headache Society criteria, headache attributed to dialysis occurs during HD, disappearing within 72 h after dialysis, and emerges in at least half of the HD sessions to make up a total of at least three attacks (ICHD-II). Studies report that HRH occurs in 27.6%–70% of patients, and an earlier study from our center revealed a 48% frequency [6–8].

There is no consensus regarding the pathophysiology of or the triggering factors for HRH. Studies have identified various underlying pathophysiological mechanisms such as type of dialysate, blood urea differences, arterial hypertension and hypotension, sodium washout, reduced serum osmolality, and low plasma renin or magnesium levels as possible contributors to this condition [8,9]. Significant differences with respect to pre- and post-dialysis results for arterial blood pressure and blood urea nitrogen (BUN) levels were found previously in a relatively small group of patients with HRH [8]. Neyer *et al*. [10] reported that headache during dialysis was more frequent and severe in patients receiving acetate dialysis than in those receiving bicarbonate dialysis, owing to metabolic acidosis.

In this prospective study, the aim was to determine the frequency, clinical characteristics of and triggering factors for HRH and to evaluate candidate preventive strategies for reducing the incidence of HRH in a large group of patients undergoing HD sessions under a standard dialysis program using bicarbonate dialysate.

Methods

A total of 494 patients with chronic renal failure who were able to report the required information concerning the presence of headache were included in this study. To meet the inclusion criteria, patients should have been on a regular dialysis program for at least 6 months at one of the two biggest dialysis clinics in the city between 1 May 2015 and 31 December 2015. The two clinics are part of the same public healthcare program, possess similar equipment and follow similar procedures and processes.

This study was approved by the Ethics in Research Committee of the local University Review Board. Each patient enrolled in this study provided written informed consent. The patients were enrolled on a random basis, i.e. on random weekdays. Patients with a previous history of any type of primary or secondary headaches or any other neurological disorders or of headaches with attacks occurring >50% of the time in between HD sessions were excluded from the study. HRH was diagnosed according to the ICHD-II criteria [11]. Patients complaining with HRH underwent extensive face-to-face physical and neurological examinations by a headache expert and responded to a semi-structured questionnaire examining the presence and clinical characteristics of headaches prior to and during the HD program. The intensity of pain was quantified using the Visual Analog Scale (VAS). In the 72 h after each HD session, patients were questioned regarding their headache experiences during the session. Amongst these patients, 275 without headache were selected to form a comparative control (CC) group. All HRH and CC patients underwent bicarbonate HD three times weekly using 1.3-m^2 hemophane membranes, and each session ultrafiltration was done up to 5% of the dry weight of the patients in the dialysis centers. The blood flow target rate was 350 ml/min, and the Kt/V target (K, dialyzer clearance of urea; t, dialysis time; V, urea distribution volume) was 1.4; over 90% of the patients achieved these two targets. The duration of the sessions was 4 h. Demographic data and etiologies of chronic renal failure in patients were confirmed by assessing the patient medical files and by consulting their nephrologists (FK, AS). Arterial systolic and diastolic blood pressure, body mass index (BMI) and serum BUN and creatinine levels were measured before and after each HD session in all patients. The urea reduction ratio (URR) during the dialysis session was also determined. URR is defined as the percentage drop in serum BUN levels from before to after the dialysis session, which is calculated using the simple formulation $1 - (\text{preBUN}/\text{postBUN}) \times 100$.

Statistical analyses were conducted using SPSS software (version 15.0). Means and standard deviations were calculated for baseline characteristics. The Student's t test (two-tailed) and Pearson's correlation analysis were used for normally distributed variables, whilst the Mann–Whitney U test and Spearman's rank correlation test were used for nonparametric variables. P values lower than 0.05 were considered statistically significant.

Results

This study included a total of 494 patients, 191 females (38.7%) and 303 males (61.3%); 219 patients

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Table 1 Demographic and etiological features of the HRH and CC groups

Table 1	Patients in the HRH group (%)	Comparative control patients (%)	Total	*P* value
	175 (38.88)	275 (61.12)	450	
Gender (F/M)	63/112	101/174	164/286	0.896
Age (years) (mean ± SD)	57.32 ± 15.75	59.79 ± 14.73	58.83 ± 15.16	0.092
Women (mean ± SD)	60.04 ± 14.83	61.89 ± 16.22	61.18 ± 15.68	0.466
Men (mean ± SD)	55.77 ± 16.11	58.57 ± 13.69	57.48 ± 14.72	0.118
BMI (mean ± SD)	25.19 ± 6.89	25.77 ± 5.26	25.54 ± 5.94	0.320
Duration of HD history (months) (mean ± SD)	73.78 ± 61.31	68.21 ± 60.40	70.38 ± 60.75	0.345
Etiology				
Hypertensive nephrosclerosis	44 (25.1%)	73 (26.5%)	117 (26.0%)	
Diabetic nephropathy	38 (21.7%)	55 (20.0%)	93 (20.6%)	
Chronic pyelonephritis	13 (7.4%)	17 (6.2%)	30 (6.7%)	
Polycystic kidney	12 (6.9%)	14 (5.1%)	26 (5.8%)	
Chronic glomerulonephritis	6 (3.4%)	15 (5.5%)	21 (4.7%)	
Unknown	62 (35.5%)	101 (36.7%)	163 (%36.2)	
Total	175 (100%)	275 (100%)	450 (100%)	0.720

(44.3%) reported headache during the HD sessions. The following patients were excluded: 19 with episodic or chronic migraine (8.7%), 14 with tension-type headache (6.4%), five with hypertensive headache (2.3%) and six with headache attacks occurring >50% of the time in between sessions (2.7%). One hundred and seventy-five patients (35.4%) with a mean age of 57.3 ± 15.7 years were diagnosed with HRH, according to the ICHD-II criteria [11]. Of these, 63 (36.0%) were females and 112 (64.0%) were males. HRH was more common in males ($P < 0.001$). The CC group included 101 (36.6%) females and 174 (62.7%) males, in total 275 patients. Details are shown in Table 1. The mean duration of the HD treatment was 73.8 ± 61.3 months for the HRH group and 68.2 ± 60.4 months for the CC group ($P = 0.345$). There was no statistically significant difference between the two groups with respect to age, sex, BMI or duration of HD treatment (Table 1).

The etiologies of end-stage renal failure in the HRH group and the CC group are also shown in Table 1. No statistically significant differences were found concerning the etiologies in each group ($P > 0.5$ for all parameters).

Headache started with a mean of 2.90 ± 0.86 h after the HD session (median 3.0 h; Table 2). The localization of pain was reported to be bifrontal in 41.7% ($n = 73$), generalized in 25.8% ($n = 45$), vertex in 13.7% ($n = 24$), bitemporal in 10.8% ($n = 19$) and occipital in 8.0% ($n = 14$) of patients; 167 patients had bilateral headaches (95.4%). The mean duration of headache was 6.22 ± 7.8 h (median 3.0 h), with a duration of ≤4 h reported by 64.0% ($n = 112$) of patients. The mean VAS score was 5.64 ± 2.05 (median 5.0). Patients reported suffering throbbing (73 patients, 41.7%), dull (69 patients, 39.4%) or stabbing pain (25 patients, 14.3%).

Table 2 Headache characteristics in HRH patients

Characteristics of the HD headache	*n* (%)
Localization of headache	
Bifrontal	73 (41.7)
Vertex	24 (13.7)
Generalized	45 (25.8)
Bitemporal	19 (10.8)
Occipital	14 (8.0)
Total	175 (100)
Comorbid symptoms of headache	
Phonophobia	74 (42.3)
Photophobia	71 (40.6)
Dizziness	60 (34.3)
Vomiting	60 (34.3)
Headache duration (h) (mean ± SD)	6.22 ± 7.8
VAS score (mean ± SD)	5.64 ± 2.05
Headache onset time during HD (h) (mean ± SD)	2.90 ± 0.86

Table 3 shows the pre- and post-dialysis BUN and creatinine levels and the URR. The differences between pre- and post-dialysis BUN values were 94.6 ± 31.1 in HRH patients and 86.8 ± 28.5 in the CC group. The difference between pre- and post-dialysis BUN values in patients with HRH was statistically significant ($P = 0.006$). The pre-dialysis systolic blood pressure was 133.7 ± 20.5 mmHg in HRH patients and 126.0 ± 22.9 mmHg in CC subjects ($P = 0.002$), and the diastolic blood pressure was 76.8 ± 13.1 mmHg in HRH patients and 70.7 ± 15.0 mmHg in CC subjects ($P < 0.001$). The post-dialysis systolic blood pressure was 111.3 ± 19.1 mmHg in HRH patients and 113.2 ± 21.9 mmHg in CC subjects, and the diastolic blood pressure was 66.2 ± 11.3 mmHg in HRH

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Table 3 Comparisons for pre-dialysis data, post-dialysis data and pre/post-dialysis data across groups

	Patients in the HRH group (%)	Comparative control patients (%)	*P* value
Pre-dialysis urea (mg/dl)	123.68 ± 38.82	113.88 ± 36.57	0.007
Post-dialysis urea (mg/dl)	29.01 ± 13.12	27.06 ± 14.15	0.142
Pre/post-dialysis urea (mg/dl)	94.67 ± 31.18	86.82 ± 28.51	0.006
Pre-dialysis creatinine (mg/dl)	9.57 ± 11.18	9.89 ± 13.05	0.794
Post-dialysis creatinine (mg/dl)	2.94 ± 2.37	3.08 ± 3.66	0.658
Urea reduction rate (%)	76.52 ± 7.46	76.29 ± 8.07	0.767
Pre-dialysis systolic blood pressure (mmHg)	133.74 ± 20.58	126.07 ± 22.97	0.002
Post-dialysis systolic blood pressure (mmHg)	111.33 ± 19.11	113.20 ± 21.96	0.411
Pre/post-dialysis systolic blood pressure difference (mmHg)	22.41 ± 16.54	12.86 ± 19.40	<0.001
Pre-dialysis diastolic blood pressure (mmHg)	76.89 ± 13.17	70.70 ± 15.00	<0.001
Post-dialysis diastolic blood pressure (mmHg)	66.26 ± 11.38	64.79 ± 13.51	0.291
Pre/post-dialysis diastolic blood pressure difference (mmHg)	10.63 ± 11.41	5.91 ± 13.17	0.001

patients and 64.7 ± 13.5 mmHg in CC subjects. The systolic blood pressure difference between the pre- and post-dialysis measurements was 22.4 ± 16.5 mmHg in HRH patients and 12.8 ± 19.4 mmHg in CC subjects ($P < 0.001$). The diastolic blood pressure difference between the pre- and post-dialysis measurements was 10.6 ± 11.4 mmHg in HRH patients and 5.9 ± 13.1 mmHg in CC subjects ($P = 0.001$). Patients with HRH had significantly higher mean systolic and diastolic blood pressure pre-dialysis values compared with CC subjects (systolic, $P = 0.002$; diastolic, $P < 0.001$). Furthermore, the differences in systolic and diastolic blood pressure between pre- and post-dialysis were higher in the HRH group ($P < 0.001$ and $P = 0.001$, respectively).

Discussion

Headache is one of the most common neurological symptoms occurring in dialysis patients, with reported frequencies ranging from 27.6% to 70% [6–8]. Although some authors report a higher frequency (50%–70%) of headache, others claim a lower rate. These discrepancies may be the result of differences in study design, case selection and dialysis protocols. To achieve a more accurate HRH frequency rate, our study was designed to include only patients on a standard bicarbonate dialysate HD protocol with a duration of 4 h and frequency of three times per week. In this study, headache occurred in 44.3% of HD patients, and HRH, classified according to ICHD-II criteria, occurred in 35.4% of patients. The prevalence of migraine was 8.7% in our patient group. The migraine prevalence in the Turkish population was reported to be 16.4% in a previous study (24.6% in females and 8.5% in males), which is higher than that in our patient group [12]. In a previous study, the prevalence of migraine and tension-type headache was found to be higher in HD patients [6]. Possible reasons for the lower rate seen in our study might be related to male predominance and the older age of our patients. The prevalence of tension-type headache was 6.4% in our patient group, which is consistent with the study by Ertas *et al.* (5.1% in the Turkish population). The ICHD-II provides criteria for headache attributed to HRH that are also noted in the recently published beta version of the ICHD-III [13]. According to the ICHD-III criteria, HRH is defined as headache that starts during HD, resolves within 72 h of HD session completion and ceases after successful transplantation [13]. The difference in criteria between the two editions is very important and could have a huge impact on the diagnosis of HRH: 'headache develops during at least half of HD sessions versus each headache has developed during an HD session'. There are limitations to those proposed criteria that require further discussion. It is likely that a debate about the suggested diagnostic criteria of HRH will continue for some time. Antoniazzi *et al.* reported that headache mostly occurs during the third or fourth hours of the dialysis session, but some studies suggest that headache increases with the duration of the dialysis session [6,14]. In our study, the dialysis duration of the patients was 4 h. Headache started at a mean of 2.90 ± 0.86 h after the initiation of the dialysis session and was experienced mostly during the third hour (68.0%).

Obviously, there are limitations to all these proposed criteria that require further discussion. It is likely that a debate about the suggested diagnostic criteria of HRH will continue for some time.

Attacks that lasted 3 h were characterized as bilateral in 95.4% and bifrontal in 41.7% of the patients. The majority of patients described their headache as moderate in severity (median VAS score was 5.0), with a throbbing (41.7%) or dull (39.4%) character. The clinical characteristics of HRH in our patients were similar to those described in previous studies

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[8,15,16]. A relationship between total years of HD and headache frequency possibly exists; however, it was observed that patients on dialysis for less than a year had a significantly lower rate of HRH (14.3%, $P = 0.037$), whereas after the first year there was a steady increase in the prevalence of HRH, which stabilized after 5 years. One of the other concerns was the question of a correlation between the frequency of dialysis and headache. Bana *et al*. have suggested that a longer interval between HD sessions could be related to a higher frequency of HRH [7]. Because our patients had three HD sessions per week on weekdays, a higher headache rate would therefore be expected during the beginning of the week. Our study was not designed to assess this parameter, and headache characteristics and incidence were questioned on random visits, neglecting these longer interval differences. Another limitation of our study was that patients were not screened specifically for depression or anxiety, which may contribute to headache development.

The pathophysiology of HRH is still debated. Roles related to renin, aldosterone, calcitonin gene-related peptide, use of different dialyzers, and changes in the biochemical profile and physiological parameters have all been proposed [7,8,17]. Another possibility is the presence of hypertension prior to the HD session or blood pressure changes during HD [7,8]. Bana *et al*. found a positive correlation between the severity of hypertension and the likelihood of headache occurring during HD. However, one of the most common complications in HD patients is hypotension which results in nausea, vomiting, muscle cramps and anxiety-related headaches. These conditions might increase the risk and severity of headache due to dialysis. One of the factors affecting dialysis-induced hypotension is the ultrafiltration ratio which also triggers the risk of complications due to HD. In our study, systolic and diastolic blood pressures before the HD session were higher in HRH patients compared with the CC group. Furthermore, the pre- and post-dialysis systolic and diastolic blood pressure differences were significantly higher ($P < 0.001$ and $P = 0.001$, respectively) in the HRH group. None of our patients' headache characteristics met the criteria for arterial hypertension. The headache might be caused by high blood pressure prior to the HD session or excessive blood pressure changes during the session. Because dialysis removes urea from the plasma more rapidly than urea can leave the brain, a very transient difference in osmolality develops across the blood–brain barrier. With an abrupt decrease in the urea blood level during HD, an osmotic gradient develops and water shifts into the brain, resulting in increased intracranial pressure, brain edema and headache [18,19]. It was also demonstrated that pre- and post-dialysis BUN values were significantly different between the two groups, suggestive of a reverse urea effect ($P = 0.006$).

In conclusion, this study, consisting of a large group of HD patients, revealed a high prevalence of HRH. HRH occurred in nearly one-third of the patients, predominantly males, during HD sessions. Headache was characterized as primarily bilateral, and either throbbing or dull, with moderate severity. Almost half of the patients reported photophobia or phonophobia concurrent with headache. This form of headache seems to be related to serum BUN levels and blood pressure differences between the pre- and post-dialysis periods. It is possible that HRH can be prevented by screening for high blood pressure and serum BUN levels prior to dialysis.

Disclosure of conflict of interest

The authors declare no financial or other conflicts of interest.

Clinical implications or article highlights

The article emphasizes the prevalance of hemodialysis-related headache and how it can be prevented.

Other

The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see
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