



Research Article

Asymptomatic Microhemorrhage In Chronic Hemodialysis Patients

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Summary

Background: The rate of intracerebral hemorrhage is higher in chronic hemodialysis (HD) patients than in the general population. Cerebral microbleeds (CMBs) detected by T2 weighted gradient-echo magnetic resonance imaging (GE-MRI) are considered as evidence of advanced microangiopathy. The aim of this study is to investigate the frequency of cerebral microbleeds (CMBs) in HD patients.

Materials and Methods: Study population consisted of volunteer HD patients followed up in Şişli Etfal Education and Research Hospital, Department of Nephrology and healthy and hypertensive controls with similar demographic features. All subjects had cranial GE-MRI for detecting CMBs.

Results: CMBs on GE-MRI were found in 8 of the patient group and in none of the controls ($p=0,005$). Twenty-two of patients (64,7%), 3 of healthy controls (11,5%) and 2 of hypertensive controls (%8,6) had leukoaraiosis respectively ($p=0,000$).

Conclusion: Asymptomatic CMBs frequently occur in HD patients and their presence might be a risk factor for hemorrhagic and ischemic stroke.

Key words: Cerebral microbleeds, hemodialysis, stroke, risk factor, leukoaraiosis

Kronik Hemodiyaliz Hastalarında Asemptomatik Mikrokanamalar

Özet

Amaç: Kronik hemodiyaliz (HD) hastalarında beyin kanaması riski toplumun geneline oranla yüksektir. T2 ağırlıklı gradient eko manyetik rezonans görüntüleme (GE-MRG) ile saptanan serebral mikrokanamalar (SMK) ilerlemiş mikroangiopatinin göstergesi olarak kabul edilmektedir. Bu çalışmanın amacı HD hastalarında serebral mikrokanama sıklığını saptamaktır.

Gereç ve Yöntem: Çalışmaya Şişli Etfal Eğitim ve Araştırma Hastanesi Nefroloji Kliniğinde izlenen ve katılmaya gönüllü olan HD hastaları alındı. Kontrol grupları benzer yaş ve cinsiyetteki sağlıklı kişilerden ve hipertansiyon hastalarından oluşturuldu. Tüm hastalara kranial T2 ağırlıklı GE-MRG yapıldı.

Sonuçlar: Hasta grubunda 8 kişide SMK görülürken kontrol gruplarında hiç kimsede mikrokanama saptanmadı ($p=0,005$). Lökoaraiozis hastaların %64,7'sinde, sağlıklı kontrol grubunun %11,5'inde, hipertansif kontrol grubunun %8,6'sında saptandı ($p=0,000$).

Sonuç: Asemptomatik SMK HD hastalarında sık görülür ve diğer bilinen risk faktörlerinin yanı sıra hem iskemik hem hemorajik inme için risk faktörü olabilir.

Anahtar Kelimeler: Serebral mikrokanamalar, hemodiyaliz, inme, risk faktörleri, lökoaraiozis

INTRODUCTION

The stroke incidence and death rate due to stroke is higher in chronic hemodialysis (HD) patients than in the general population^(11,17) and intracerebral hemorrhage is the most frequent type⁽¹⁰⁾.

Cerebral microbleeds (CMBs) are seen as small round hypointense lesions on T2-weighted gradient-echo magnetic resonance imaging (GE-MRI) and correspond histopathologically to deposits of hemosiderin from previous bleeding^(2,6). CMBs are found in 4,5-7,7% of healthy population⁽¹³⁾. Asymptomatic CMBs were observed to occur more frequently in patients with recurrent stroke either hemorrhagic or ischemic and was strongly associated with the severity of leukoaraiosis⁽¹⁶⁾.

A previous retrospective study where we analyzed our clinical data about multiple CMBs seen in chronic hemodialysis patients lead the basis for this prospective study⁽¹⁸⁾. In this group of patients, detecting microangiopathies prone to hemorrhage is extremely important.

In order to determine the relationship between CMBs and chronic HD, we prospectively recruited HD patients in a case control design and aimed to investigate the relationship between them.

MATERIAL AND METHODS

Study population consisted of volunteer HD patients followed up in Şişli Etfal Education and Research Hospital, Department of Nephrology, who had no past history or symptoms of stroke and no contraindication for cranial magnetic resonance imaging (MRI) examination (such as pacemaker or metallic prosthesis insertion, and claustrophobia).

After obtaining informed consent, 34 patients were enrolled for the study.

Control groups consisted of 29 consecutive consenting healthy individuals presenting

to the primary care clinic for a routine physical examination and 23 hypertensive patients presenting to the hypertension outpatient clinic with similar demographic features.

Determination of major vascular risk factors was based on history and laboratory findings. Hypertension was considered present when a patient had received antihypertensive treatment before admission or when hypertension was diagnosed during the hospital stay by repeated detection of blood pressure 140/90 mmHg. A diagnosis of diabetes mellitus (DM) was based on a history of DM with or without current treatment or two fasting plasma glucose levels of 126 mg/dL or higher. A diagnosis of hypercholesterolemia was based on history of hypercholesterolemia with medication or a fasting serum cholesterol level > 220 mg/dL. A history of smoking was coded if a subject was a current smoker or an ex-smoker who had quit smoking 5 years of admission. Alcohol was accepted as a risk factor if current consumption reached to 300g/week.

MRI examination of brain was performed on 1,5-T superconducting magnet with a standard head coil (Signa Excite 2.0, GE Healthcare). The protocol included initial acquisition of a scout image (repetition time msec/echo time msec, 15/6), followed by application of the following sequences: T1-weighted spin echo (575/14; section thickness, 6 mm; field of view, 210 mm; matrix, 256 x 256), T2-weighted fast spin echo (2,474/17, 102; section thickness, 6 mm; field of view, 210 mm; matrix, 256 x 256), axial T2-weighted gradient-echo sequences (TR/TE 640/15 msn, flip angle 15°), fluid-attenuated inversion recovery (FLAIR) (repetition time msec/echo time msec/inversion time msec, 9,000/110/1,800; section thickness, 5 mm; field of view, 240 mm; matrix, 256 x 256).

Focal areas of homogeneous round signal loss in brain parenchyma measuring <

5mm areas on GE-MRI sequences were identified as CMBs. The number of CMBs was counted on whole brain area by 2 authors (D.N O and E.U) separately and determined by consensus. Lesions within the sulcal areas and areas of symmetric hypodensity of globus pallidus, likely to represent adjacent pial blood vessels and calcification respectively, were not included. We classified the degree of CMBs as absent, mild (1-5), moderate (5-10) and severe (>10) described by Lee et al⁽¹⁵⁾. Leukoaraiosis was classified as punctuate, early confluent, and confluent by using the method described by Fazekas et al⁽⁵⁾.

For all patients the duration of HD was recorded and patients were grouped as with short HD duration (1-5 years) and long HD duration (>5 years).

Descriptive and frequency statistical analysis were obtained and comparisons were made using the SPSS 17.0 statistical package. Evaluation of the data was by definition of mean $\pm$ SD. Comparisons for clinical variables between patients and controls were performed by using unpaired t-test and Chi-square test as appropriate. The threshold level for statistical significance was established at $p < 0.05$.

RESULTS

The mean age ($\pm$ SD) of patients, healthy and hypertensive controls were $48,74 \pm 15,93$, $52,93 \pm 13,21$ and $49,35 \pm 7,32$

years, respectively. Nine of patients (26,4%), 12 of healthy controls (41,37%) and 16 of hypertensive controls were females. No significant differences in the distribution of age were found between patients and the control groups ($p = 0,26$ and $p = 0,89$ respectively). Also no significant differences in the distribution of gender were found between patients and healthy controls ($p = 0,21$), but there were more female in hypertensive control group ($p = 0,01$).

CMBs on GE-MRI were found in 8 of the patient group and in none of the controls ($p = 0,005$). The degree of CMBs was mild in all patients. There was not a significant difference between risk factors of patients with and without CMBs (Table-1). Twenty-two of patients (64,7%), 3 of healthy controls (11,5%) and 2 of hypertensive controls (%8,6) had leukoaraiosis respectively ($p = 0,000$). From 8 patients with CMBs, 7 had leukoaraiosis. The mean duration of HD was $3,50 \pm 2,26$ and $3,09 \pm 2,65$ years in patients with and without CMBs respectively. There was not a significant difference between patients with and without CMBs regarding HD duration ($p = 0,70$). From 12 patients with long HD duration, 11 had leukoaraiosis. Eleven of 22 patients with short HD duration had leukoaraiosis and the difference between groups was significant ($p = 0,02$).

Table 1: Demographic features of patients with and without cerebral microbleeds

	CMB(-) (n=26)	CMB(+) (n=8)	P value
Hypertension	15	6	0,34
DM	4	7	0,60
Cardiac diseases	7	1	0,64
Antiplatelet therapy	5	2	0,64
Alcohol	1	0	1,0
Smoking	14	4	1,0
Hyperlipidemia	7	3	0,66
Obesity	2	1	1,0
Disease duration			
1-5 years	18	4	0,41
>5 years	8	4	
Leukoaraiosis	15	7	0,12

CBMs = Cerebral microbleeds

DM= Diabetes mellitus

DISCUSSION

In the present study, we evaluated frequency of CMBs in HD patients and we found that the incidence of CMBs were significantly higher than controls. In addition there was a correlation between leukoaraiosis and CMBs.

CMBs detected by GE-MRI are considered evidence of advanced microangiopathy with potential for further bleeding^(6,21,26). Asymptomatic CMBs were observed not only in patients with ICH^(7,26) but also in patients with ischemic stroke^(4,14) and occur more frequently in patients with recurrent stroke either hemorrhagic or ischemic^(1,28). Old CMBs provide further evidence of severe microangiopathy with a subsequent increased vascular vulnerability⁽¹⁹⁾. Roob et al. found CMBs in 6% of 280 healthy people and they were associated with advancing age, hypertension and leukoaraiosis⁽²⁵⁾. Incidence of CMBs in the population-based Rotterdam Scan Study over a 3-year interval was 10%⁽²⁰⁾.

The higher incidence of hypertensive ICHs in HD patients is a well known phenomenon⁽¹⁰⁾. In HD patients, ICH was

found to be more severe in terms of hematoma size and with association of intraventricular hemorrhage. The mortality rate was nearly twice than the non-HD patients⁽²²⁾. Fan et al. showed that CMBs might be an important risk factor for subsequent ICH among patients with acute ischemic stroke either⁽⁴⁾. Kidwell et al also found that in patients undergoing thrombolysis, old asymptomatic microbleeds were visualized at the site of the subsequent hemorrhage⁽¹²⁾. Thus, CMBs might be an important marker for predicting cerebral hemorrhage in HD patients.

There were two previous studies that showed that HD patients had a significantly higher incidence of microbleeds^(29,30). Like our study, they did not find a correlation between the duration of HD and the presence of microbleeds. They suggested that higher incidence of microbleeds are not caused by HD but by other factors, such as hypertension⁽²⁹⁾. In our study CMBs are significantly higher in HD patients than hypertensive controls. In a recent study, Cho et al. found that decreased kidney function was associated

with CMBs in patients with acute ischemic stroke⁽³⁾. This association was independent of other risk factors, and the number of CMBs increased as the glomerular filtration rate level decreased⁽³⁾. Kidney and brain are end organs and their vascular beds have very low resistance and are passively perfused at high flow throughout systole and diastole⁽²⁴⁾. Although because of the hemodynamic similarities between vascular beds of the kidney and the brain they are vulnerable to hypertensive damage, CMBs in HD patients seems to be independent of hypertension.

In general, stroke patients with CMBs were significantly older, hypertensive, diabetic, and had more lacunar infarcts and leukoaraiosis^(13,19). In this study, we found that only leukoaraiosis was significantly associated with CMBs in HD patients among vascular risk factors. Previous studies have revealed that CMBs were associated with leukoaraiosis^(9,16,23,27). In a population based study, Ikram et al. found that cerebral small vessel diseases such as lacunar infarcts and leukoaraiosis were associated with impaired kidney function⁽⁸⁾. Either rupture or occlusion associated with microangiopathy might result in intracerebral hemorrhage or ischemic stroke depending on circumstances⁽¹⁶⁾. In HD patients, uremia or HD might contribute to the progression of microangiopathy⁽³⁰⁾.

Although we found that the incidence of CMBs was not related to the duration of HD, it is difficult to comment on this relation because of our small sample size. Nevertheless the incidence of leukoaraiosis in HD patients was related to the duration of HD.

In conclusion, asymptomatic CMBs shown by GE-MRI frequently occur in HD patients and the presence of CMBs might be a risk factor for hemorrhagic and ischemic stroke besides other well known risk factors. We propose that, it would be possible to identify those who were likely to experience future strokes by scanning

HD patients for CMBs. Further larger sample prospectively designed studies are needed.

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