CLINICS

CLINICAL SCIENCE

The level of circulating endothelial progenitor cells may be associated with the occurrence and recurrence of chronic subdural hematoma

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OBJECTIVES: The onset of chronic subdural hematoma may be associated with direct or indirect minor injuries to the head or a poorly repaired vascular injury. Endothelial progenitor cells happen to be one of the key factors involved in hemostasis and vascular repair. This study was designed to observe the levels of endothelial progenitor cells, white blood cells, platelets, and other indicators in the peripheral blood of patients diagnosed with chronic subdural hematoma to determine the possible relationship between the endothelial progenitor cells and the occurrence, development, and outcomes of chronic subdural hematoma.

METHOD: We enrolled 30 patients with diagnosed chronic subdural hematoma by computer tomography scanning and operating procedure at Tianjin Medical University General Hospital from July 2009 to July 2011. Meanwhile, we collected 30 cases of peripheral blood samples from healthy volunteers over the age of 50. Approximately 2 ml of blood was taken from veins of the elbow to test the peripheral blood routine and coagulation function. The content of endothelial progenitor cells in peripheral blood mononuclear cells was determined by flow cytometry.

RESULTS: The level of endothelial progenitor cells in peripheral blood was significantly lower in preoperational patients with chronic subdural hematomas than in controls. There were no significant differences between the two groups regarding the blood routine and coagulation function. However, the levels of circulating endothelial progenitor cells were significantly different between the recurrent group and the non-recurrent group.

CONCLUSIONS: The level of circulating endothelial progenitor cells in chronic subdural hematoma patients was significantly lower than the level in healthy controls. Meanwhile, the level of endothelial progenitor cells in recurrent patients was significantly lower than the level in patients without recurrence. Endothelial progenitor cells may be related to the occurrence and recurrence of chronic subdural hematoma.

KEYWORDS: Chronic Subdural Hematoma; Endothelial Progenitor Cell; Injury.

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INTRODUCTION

Chronic subdural hematomas (CSDHs) are common neurosurgical occurrences in intracranial hematoma, with an incidence ranging from 1-13.1%. Their mortality amounts to 1.5%~8%, and the recurrence rate is 9.2%-26.5% (1-6). The pathogenesis of CSDH remains hypothetical. There has been significant discussion and debate regarding the complex pathogenesis of CSDH, particularly in terms of the inflammatory process (7), the head trauma etiology (8,9), the osmotic gradient theory (10-12), and recurrent hemorrhage associated with hyperfibrinolysis (13).

The onset of CSDH may be associated with direct or indirect minor injury of the head or poor vascular repair. Accordingly, there are a large number of brittle neovascular capillaries in the outer membrane of the resulting hematoma, and continuous leaking from these structural capillary defects is the main reason for the development of CSDH. The outer membrane of the hematoma capsule generally contains numerous fragile macrocapillaries (also called sinusoidal vessels) with vascular lumina (14). When viewed with an electron microscope, these lumina are often extremely wide ($\geq$ 40 μm in diameter), contain several blood cells and consist

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of loose junctions between adjacent endothelial cells and a partial absence of the basement membrane and pericytes (15).

Endothelial progenitor cells (EPCs) happen to be one of the key factors involved in hemostasis and vascular repair. These cells, through the secretion of related cytokines, play an extremely important role in the repair and regeneration of damaged blood vessels. Therefore, we observed the levels of EPCs, white blood cells, platelets, and other indicators in the peripheral blood of CSDH patients to determine the possible relationship between EPCs and the occurrence, development, and outcomes of CSDH.

MATERIALS AND METHODS

Patients

We collected clinical information from 30 patients who were diagnosed with CSDH by computer tomography (CT) scanning and operating procedures at Tianjin Medical University General Hospital from July 2009 to July 2011. Sixteen patients had clear histories of minor head trauma in the last year before they were diagnosed with CSDH. All patients underwent a single burr-hole drainage surgery under local anesthesia. Four cases relapsed and recovered after reoperation. We collected peripheral blood samples 2 hours prior to the surgery and 14 days after the surgery. Meanwhile, over the same period, we collected peripheral blood samples from 30 healthy volunteers over the age of 50. Head CT scans were performed at Tianjin Medical University General Hospital in the Division of Radiology. Patients who had diabetes (16), dyslipidemia, intractable hypertension coronary heart disease, kidney disease (17), or hemorrhage disease (18) were classified as exclusions. No estrogen or anticoagulant agents were used in either group due to their potential influence on EPC levels (19,20).

Laboratory management

We took approximately 2 ml of blood from the veins of the elbow, immediately placed it in EDTA-K2 anticoagulation tubes, and gently mixed it upside down to prevent platelet adhesion and aggregation. Peripheral blood routine and coagulation function were tested by Tianjin Medical University General Hospital, Department of Clinical Laboratory (automatic biochemistry analyzer: SYSMEX XE-2100, Sysmex Corporation, Japan).

Because EPCs are characterized by the co-expression of the hematopoietic stem cell/progenitor markers CD34 and CD133 (21,22), we determined the content of EPCs in peripheral blood mononuclear cells (PBMNCs) by flow cytometry using dual staining with fluorescein-conjugated monoclonal antibodies against CD34/CD133 markers. PBMNCs were isolated by density centrifugation according to the manufacturers' instructions. We incubated 10^6 PBMNCs with PE-labeled monoclonal mouse anti-human CD34 (BD Biosciences, USA) and FITC-labeled monoclonal mouse anti-human CD133 (BD Biosciences, USA) antibodies for 30 minutes at 4℃, according to the manufacturers' instructions. At least 100,000 events were acquired in the lymphomonocytic gate using a FACSCalibur cytometer (BD FACS Aris, USA). The number of progenitor cells was expressed as a percentage of all lymphomonocytic cells.

Statistics

Chi-square tests or Student's T tests were used to compare categorical and continuous variables among the groups. Experimental data are presented as means ± SD. Statistical analyses were performed using commercially available software (SPSS, ver. 18.0, SPSS Inc., Chicago, IL), and a p-value of <0.05 was deemed to indicate statistical significance.

Ethics

The study was approved by the Tianjin Medical University General Hospital ethical standards committee on human experimentation. Written informed consent was also obtained from both patients and control participants.

RESULTS

In this study, we first evaluated the EPC levels in CSDH patients treated with burr-hole drainage surgery and their association with blood routine and coagulation function. The CT scan performance of CSDH is a lunula or crescent-shaped lower-density area under the skull plate on one or both sides. High- or hybrid-density shadows occurred when the hematoma volume was large, slowly absorbed, or bleeding recurrently. The demographic characteristics of the patient and control groups are summarized (Table 1). The patients ranged in age from 45 to 82 years (average 60.8±14.4 years, means±SD). There were 22 men and 8 women. All of the CSDH cases underwent burr-hole surgery. All hematoma removal cases were irrigated with saline solution in the subdural space. The control group ranged in age from 52 to 75 years (average 64.2±8.5 years, means±SD). There were 16 men and 14 women. No significant differences in age and gender between the CSDH and control groups were identified.

The average number of circulating EPCs in preoperational CSDH patients was 43.43±11.87 per 2×10^5 mononuclear cells. The average number of circulating EPCs in the health control group was 64.62±15.32 per 2×10^5 mononuclear cells. The EPC levels in the peripheral blood were significantly lower in preoperational CSDH patients than in controls ($p=0.013$). Compared with the control group, the numbers of EPCs in males, premenopausal females, and postmenopausal females of the CSDH group differed significantly ($p<0.05$). Within the CSDH or control groups, the number of EPCs in premenopausal females was higher than in the male group or in the postmenopausal female group ($p<0.05$). Meanwhile, there was no difference between the male group and the postmenopausal female group. There were no significant differences between the CSDH group and the control group or between males and females within the same group regarding any indices of blood routine and coagulation, such as red blood cell (RBC), white blood cell (WBC), platelet (PLT), and hemoglobin (Hb) levels; prothrombin time (PT); prothrombin time-international normalized ratio (PT-INR); activated partial thromboplastin time (APTT); and thrombin time (TT) (Table 1).

Six of the 30 CSDH patients suffered recurrences after the burr-hole drainage operation, and all of them underwent the surgical treatment again, achieving good recovery. The change in the average level of circulating EPCs in the six recurrent patients was 8.54±5.25 per 2×10^5 mononuclear cells between postoperation and preoperation. The same index in the other nonrecurring patients was 35.52±18.59 per 2×10^5 mononuclear cells. The difference was significant

Table 1 - Laboratory characteristics of patients and controls.

	CSDH Patients (n = 30)			Controls (n = 30)		
Age	60.8 ± 14.4			64.2 ± 8.5		
Gender	Male	Female		Male	Female	
		Premenopausal	Postmenopausal		Premenopausal	Postmenopausal
	22	3	5	16	5	9
Number of EPCs	37.74 ± 10.47a	62.28 ± 10.49a.b.c	38.12 ± 10.37a	52.58 ± 14.24	70.47 ± 9.37b.c	53.18 ± 16.38
Preoperation (/2*10^5 MNC)		43.43 ± 11.87[a]			64.62 ± 15.32	
Blood Routine						
RBC (×10^{12})	4.63 ± 0.45	3.85 ± 0.53		4.71 ± 0.64	3.92 ± 0.43	
WBC (×10^9)	8.52 ± 2.62	8.36 ± 2.41		7.93 ± 1.12	7.61 ± 1.03	
PLT (×10^9)	236.24 ± 71.45	226 ± 82.49		251.45 ± 46.39	255.93 ± 55.29	
Hb (×10^9)	134.28 ± 17.23	123.46 ± 18.38		128.46 ± 16.24	121.35 ± 18.34	
Blood Coagulation						
PT (sec)	11.58 ± 0.41	11.01 ± 0.62		11.46 ± 0.53	11.02 ± 0.42	
PT-INR	0.962 ± 0.031	0.931 ± 0.025		0.960 ± 0.031	0.943 ± 0.027	
APTT (sec)	29.63 ± 6.39	27.38 ± 5.47		32.29 ± 4.63	29.48 ± 4.92	
TT (sec)	15.95 ± 2.62	16.21 ± 2.95		17.28 ± 1.61	15.96 ± 2.41	

Values are means ± SD. CSDH = chronic subdural hematoma; EPCs = endothelial progenitor cells; MNC = mononuclear cell; RBC = red blood cell; WBC = white blood cell; PLT = platelet; Hb = hemoglobin; PT = prothrombin time; PT-INR = prothrombin time-international normalized ratio; APTT = activated partial thromboplastin time; TT = thrombin time.
*T tests were used to compare continuous variables among groups if the data followed a normal distribution; otherwise, nonparametric tests were used. Chi-square tests were used to compare categorical variables among the groups. a: Compared to the control group, $p<0.05$; b: Compared to males in the same group, $p<0.05$; c: Compared to postmenopausal women in the same group, $p<0.05$.

between the recurrent group and the non-recurrent group ($p = 0.008$) (Table 2).

DISCUSSION

In recent years, EPCs, especially in the peripheral blood, have become the focus of research in the field of related blood vessels. EPCs are immature hematopoietic cells circulating in the peripheral blood that are capable of differentiating into mature endothelial cells, thus aiding in endothelial recovery (23). Small numbers of EPCs are circulating in the peripheral blood of every healthy adult, approximately 70-210/ml, accounting for 0.002% of PBMNCs (24). EPCs are involved not only in the formation of new blood vessels but also in the maintenance of the dynamic integrity of vascular membrane; thus, they play an important role in physiological repair. EPCs participate in these processes through mobilization, tendency, adhesion, proliferation, and differentiation. Any pathological and physiological factors resulting in reduced numbers of EPCs and fewer dysfunctions may lead to structural and functional abnormalities during neovascularization. Structural integrity and functional abnormalities during neovascularization lead to extravasation of the blood, increasing the likelihood of bleeding. Currently, it is generally accepted that the adventitial neovascularization of hematomas and re-bleeding are key factors in the onset and development of CSDH (25). Thus, EPC reduction may be relevant to CSDH.

Table 2 - Number of EPCs 14 days after operation.

	Recurrence	No recurrence	*p*-value*
Number of CSDH Patients	6	24	NS
Number of EPCs (/2*10^5 MNC)	8.54 ± 5.25[a]	35.52 ± 18.59	0.008

Values are means ± SD. CSDH = chronic subdural hematoma; EPCs = endothelial progenitor cells; *T tests were used to compare continuous variables among groups if the data followed a normal distribution; otherwise, nonparametric tests were used. Chi-square tests were used to compare categorical variables among groups. [a]Compared to no recurrence, $p<0.05$. NS = non-significant.

CSDH mainly occurs in the elderly. The incidence rate in the population over 65 years of age is 7-13/10 million, and the rate in people over 70 years of age is 17-58/10 million (26). However, the CSDH incidence in the general population is only approximately 1-3/10 million (26,27). Aging can lead to a reduction in the number of EPCs in circulation and a weakening of their function (28-30). Thus, we can infer that there are both lower numbers of EPCs and related dysfunction in the peripheral blood of CSDH patients. In this study, we measured the peripheral blood levels of EPCs in 30 CSDH patients and in 30 healthy controls. The results showed that the level of peripheral blood EPCs in CSDH patients was significantly lower compared to the control group. Meanwhile, we found that the change in the levels of EPCs in recurrent patients between postoperation and preoperation was significantly lower than the level in non-recurrent patients. These data indicate that a higher consumption of EPCs in CSDH patients and decreased EPC levels may lead to a reduced capacity to repair the endothelium, increasing the risks associated with the occurrence and recurrence of CSDH. Thus, we propose that a pharmacological means of increasing the number of circulating EPCs could help to reduce the recurrence rate of CSDH.

Through in-depth research on angiogenesis mechanisms and EPCs, we can be sure that EPCs are not only involved in the formation of new blood vessels but that they also play an important role in maintaining the dynamic integrity of the vascular intima. Any factors leading to a reduction in the number of EPCs may result in structural and functional abnormalities in the neovascularization process. Throughout our study, the levels of EPCs in the peripheral blood of patients with CSDH were significantly lower compared to the control group, and the levels of peripheral EPCs in the patients with postoperative recurrence were

significantly lower than in patients who did not relapse. Therefore, we believe that the occurrence and development of CSDH may be involved in numerous aspects of the reduction in the number of EPCs in the peripheral blood. At the very least, this reduction plays an integral role in many factors. Thus, we put forward the following hypothesis. When trauma causes a split in the dural border cell layer to form a substantial subdural hematoma, cerebrospinal fluid (CSF) and/or blood accumulates as foreign matter, stimulating the inflammatory response and resulting in the secretion of inflammatory cytokines (31-34), vascular endothelial growth factor (VEGF) (35), and angiopoietins (36,37). Similar to granulation tissue, the purpose of new blood capillaries and the outer membrane is to wrap and absorb local foreign bodies and to promote healing.

If the number of circulating EPCs is reduced and/or bone marrow-derived EPCs cannot replenish their consumption, capillary structural defects will occur. At the same time, in the case of abnormal cerebral pulsations causing new damage to the capillaries, both the maintenance of the intimal integrity and physiological repairs cannot be completed. With these internal circles, the continuous resulting effusion from pathologically permeable capillary walls into the subdural space leads to the formation of a CSDH and its eventual expansion.

In this study, we conclude that the level of circulating EPCs in CSDH patients was significantly lower than the level in healthy controls. Additionally, the level of EPCs in recurrent patients was significantly lower than the level in patients without recurrence. Thus, we speculate that the low level of EPCs may be responsible for the occurrence of CSDH; furthermore, the continuing low level of EPCs may be associated with the recurrence of CSDH.

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■ AUTHOR CONTRIBUTIONS

Song Y was in charge of the experimental design and English version of the manuscript. Wang Z was responsible for the collection and testing of blood samples. Liu L was responsible for the experimental data statistics. Wang D was responsible for the collection of clinical data. Zhang J was in charge of the overall design and adjustment of the research.

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