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Correlation of vascular endothelial growth factor with magnetic resonance imaging in chronic subdural hematomas

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ABSTRACT

Background: Chronic subdural hematoma (CSDH) is an inflammatory angiogenic disease. It is believed that vascular endothelial growth factor (VEGF) plays an important role in pathological CSDH angiogenesis.
Methods: In this study, magnetic resonance imaging (MRI) results were used to assign 115 primary CSDH patients to four MRI types. The four MRI types are described as follows: type 1 (T1-weighted low, T2-weighted low), type 2 (T1-weighted high, T2-weighted low), type 3 (T1-weighted mixed, T2-weighted mixed), and type 4 (T1-weighted low/high, T2-weighted high). The four MRI types were then correlated with CSDH stage and patient hematoma fluid and serum VEGH concentrations that were measured using an enzyme-linked immunosorbent assay (ELISA). Neurological status was assessed by Markwalder scoring at admission and six-month follow-up.
Results: The mean VEGF concentration was significantly higher in CDSH hematoma fluid samples than in patient sera ($p < 0.01$). In unilateral CSDH hematoma fluid samples, VEGF concentration was highest in type 1 (21,613.5 ± 1473.3 pg/ml), next highest in type 2 (18,071.8 ± 1737.1 pg/ml), lower in type 3, and lowest in type 4 patients (13,153.7 ± 3854.4 pg/ml, 7265.7 ± 726.2 pg/ml, respectively). High VEGF concentrations strongly correlated with MRI type (unilateral CSDH group $r = 0.838$, bilateral CSDH group $r = 0.851$, $p < 0.01$). Moreover, higher hematoma fluid VEGF concentrations correlated with markedly higher recurrence in type 1 (3/19, 15.8%) vs. type 4 unilateral CSDH patients (1/27, 3.7%).
Conclusions: The present study reports a significant correlation between CSDH hematoma fluid VEGF concentration and MRI results. Therefore, MRI results could be used to predict hematoma fluid VEGF concentrations in CSDH patients.

1. Introduction

Chronic subdural hematoma (CSDH), a common disease, is associated with substantial morbidity and mortality [1–3]. The pathogenic mechanism of CSDH initiation is very complex; pathological vascular proliferation, release of inflammatory mediators, and coagulation abnormalities each may play a role [4–7]. After formation of the hematoma capsule, pathological proliferation and rupture of blood vessels are main factors involved in CSDH progression. VEGF, a key factor in the growth and maturation of blood vessels, has been implicated in the expansion of pathological angiogenesis [8–11] and several studies have reported that the concentration of VEGF is higher in hematoma fluid than in serum [12–16]. Moreover, anti-angiogenic drugs have been demonstrated to be effective treatments for CSDH patients [17–21]. The studies also reported that the drug is not for all patients are effective [19,22,23]. So we need a predict method to select the appropriate drug treatment of patients.

Notably, one study reported that CT imaging results may be predictive of VEGF concentrations in hematoma fluid [24]. Because MRI is currently the most effective screening method for clinical staging of hematomas and is superior to CT for early hematoma evaluation, MRI results were correlated to CSDH hematoma fluid VEGF concentration. In our previous study we had observed such a correlation, but the sample size was very small [25]. In the present study using a larger sample size, we repeated our earlier investigation and expanded our study to address possible correlations of MRI and VEGF results with CSDH recurrence. We found that CSDH could be "maturity staged" using MRI imaging results and confirmed that VEGF concentration did correlate with MRI stage. These results should provide a foundation for better

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treatment of CSDH and improved prediction of CSDH prognosis. Moreover, it could help us select appropriate patients for drug therapy and change the clinical management of the patients.

2. Materials and methods

2.1. Patients

In this study, we collected data from 124 patients who were surgically treated for CSDH at The First Hospital of Jilin University between March 2013 and March 2016. Four patients were excluded due to hepatic and hematologic disease. Five patients received incomplete follow-up or were lost to follow-up, while 76 males and 39 females ranging in age from 43 to 85 years (mean age 63.8 ± 5.1 years) were included. All CSDH patients were evaluated for appropriateness of surgical intervention using computed tomography (CT) and MRI. All surgical candidates received burr-hole irrigation under general anesthesia. Serum samples were drawn preoperatively into serum separator tubes (Vacutainer, Becton Dickinson, NJ, USA) and allowed to stand for 30 min at room temperature to ensure full clotting. Hematoma fluid was collected into evacuated tubes after opening of the outer hematoma membrane. All samples were centrifuged at 3000 × *g* for 10 min and supernatants were collected and stored at −80 °C until assayed. Written informed consent for participation in the study was obtained from all participants or their guardians. We evaluated the clinical courses and outcomes and the data included patient information and recurrence rate. All patients underwent six-month follow-up. This study was approved by the Institutional Review Board (IRB) of The First Hospital of Jilin University (IRB00008484).

2.2. Measurement of VEGF by ELISA

We measured the concentration of VEGF in hematoma fluid and serum samples using commercially available solid phase ELISA kits (R&D Systems Inc., MN, USA) according to the manufacturer's instructions. All measurements were performed in duplicate. The experimenter was blinded to patients' clinical data.

2.3. Statistical analysis

Results are expressed as the mean ± SD. The paired *t*-test was applied to assess possible differences in VEGF levels between hematoma fluid and serum samples. ANOVA was employed to examine the differences between the groups based on MRI type. Correlations between the various measured parameters were determined by calculation of Spearman's rank correlation coefficients. For all statistical tests, the level of significance was set to 0.05. Statistical analysis was performed using SPSS software (SPSS Inc. SPSS Statistics for Windows, Version 17.0. Chicago, IL, USA).

3. Results

Patient epidemiological and clinical data are shown in Tables 1. In Fig. 1, MRI scans were analyzed and categorized into the four MRI result types by radiologists blinded to VEGF levels: type 1 (T1-weighted low, T2-weighted low), type 2 (T1-weighted high, T2-weighted low), type 3 (T1-weighted mixed, T2-weighted mixed), and type 4 (T1-weighted low/high, T2-weighted high). Numbers of unilateral CSDH patients of each type were: 19 type 1, 32 type 2, 25 type 3, and 27 type 4. Numbers of bilateral CSDH patients of each type were: 6 type 1, 7 type 2, 4 type 3, and 7 type 4.

There was a predominance of males vs. females, with a ratio of 1.9 to 1. The mean age of participants was >60 years of age (mean age 63.8 ± 5.1 years, range 43–85 years). The incidence of recurrence was 5.8% in patients with unilateral CSDH (6/103). There was a markedly higher recurrence rate in type 1 (3/19, 15.8%) vs. type 4 (1/27, 3.7%) unilateral CSDH patients. Eighteen patients received anticoagulant/antiplatelet therapy before operative (18/115, 15.7%). The mean age, sex ratio, and Markwalder scores were not significantly different among the four MRI types ($p > 0.05$).

3.1. ELISA analysis of VEGF

The mean concentrations of VEGF in hematoma fluid and serum patient samples are shown in Table 1. Levels of VEGF were significantly higher in hematoma fluid than in serum samples ($p < 0.01$).

3.2. Hematoma fluid VEGF concentrations in the four MRI types

The average hematoma fluid VEGF concentration was highest in type 1 patients (21,613.5 ± 1473.3 pg/ml), while type 2 patients exhibited comparably high levels of VEGF (18,071.8 ± 1737.1 pg/ml). The concentration of VEGF was markedly lower in type 3 and was lowest in type 4 patient samples (13,153.7 ± 3854.4 pg/ml, 7265.7 ± 726.2 pg/ml, respectively; Table 1). We then related hematoma fluid VEGF concentrations among the different MRI types to the rebleeding (recurrence) data previously published by Kaminogo et al. [26]. Respective data for all patients are shown in Fig. 2. Rebleeding rate and VEGF concentrations proved to be clearly related, yielding a significant correlation ($r = 0.838$; $p < 0.01$). Moreover, these results are consistent with those of our previous study [25]. At the same time, here we also analyzed the concentration of VEGF in hematoma fluid in 12 patients with bilateral CSDH (Fig. 3). In Table 2, Seven bilateral patients had the same image type on both sides (7/12, 58.3%). In these bilateral patients, however (Fig. 4), MRI type did predictably correlate with hematoma fluid VEGF concentrations ($r = 0.851$, $p < 0.01$).

Table 1
Clinical features and concentration of VEGF of unilateral CSDH patients by MRI classification ($n = 103$).

Clinical data	Type 1	Type 2	Type 3	Type 4	*p*-Value
Case	19	32	25	27	
Age (yrs)	62.9 ± 3.1	65.7 ± 5.4	62.5 ± 4.3	63.1 ± 6.5	0.63
Gender (F/M)	5/14	11/21	7/18	11/16	0.71
Antiplatelet/anticoagulation (%)	3 (15.8)	5 (15.6)	4 (16.0)	4 (14.8)	0.98
Pre Markwalder score	1.6 ± 0.4	1.6 ± 0.7	1.6 ± 0.3	1.7 ± 0.2	0.69
Post Markwalder score	0.7 ± 0.3	0.6 ± 0.5	0.7 ± 0.4	0.6 ± 0.2	0.81
MRI T1-weighted	Low	High	Mixed	Low/High	
MRI T2-weighted	Low	Low	Mixed	High	
Recurrent (%)	3 (15.8)	3 (9.4)	2 (8.0)	1 (3.7)	0.16
Hematoma fluid VEGF (pg/ml)	21,613.5 ± 1473.3*	18,071.8 ± 1737.1*	13,153.7 ± 3854.4*	7265.7 ± 726.2*	0.009*
Serum VEGF (pg/ml)	317.5 ± 22.9	337.2 ± 46.1	340.7 ± 28.3	328.9 ± 36.4	0.84

Pre, preoperation; Post, postoperation; VEGF, vascular endothelial gowth factor; CSDH, chronic subdural hematoma.
* $p < 0.05$.