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Elevated hemoglobin is associated with cerebral infarction in Tibetan patients with primary hemorrhagic neurovascular diseases

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ABSTRACT

Objectives: Although many studies have focused on primary hemorrhagic neurovascular diseases (PHNVDs) in different races, studies of PHNVDs in the plateau area of China are still insufficient. Chinese Tibetan people are the largest population living in the plateau area. Previous studies have shown that Tibetan PHNVD patients have a significantly higher incidence of cerebral infarction, but the mechanism remains uncertain. This study aimed to develop a better understanding on the mechanism of their high risk of cerebral infarction.

Patients and methods: In this retrospective case control study, we used a hospital information system to search for consecutive Tibetan patients with PHNVDs from January 2012 to June 2016. Intra-hospital data including baseline information and complications were recorded, and the risk factors for cerebral infarction were analyzed.

Results: Univariate analysis and cox proportional hazard multivariate regression analysis revealed that elevated hemoglobin (HGB) concentration was positively associated with an increased incidence of cerebral infarction ($P < 0.001$). The cutoff value that maximized the ability to predict in-hospital infarction in Tibetans with PHNVDs was 15.2 g/dL. Tibetan PHNVD patients with an increased HGB concentration were more likely to present with cerebral infarction within the first 5 days after onset of PHNVDs, and the probability was highest on the 3rd day.

Conclusions: HGB levels could be used to predict in-hospital cerebral infarction in Tibetan patients with PHNVDs. These patients are more likely to develop in-hospital infarction when the HGB concentration is higher than 15.2 g/dL. For Tibetan PHNVD patients with an elevated HGB concentration, most cerebral infarctions occurred within the first five days after onset, with more incidents occurring on the third day.

1. Introduction

Primary hemorrhagic neurovascular diseases (PHNVDs) refer to any hemorrhagic events that occur in the central nervous system, mainly including aneurysmal subarachnoid hemorrhage (aSAH), spontaneous intracerebral hemorrhage (sICH) and hemorrhagic arteriovenous malformation (AVM). These events are challenging for neurosurgeons due to their high rates of morbidity and poor prognoses [2,15,19,29,33].

Although many studies have focused on PHNVDs in different races, studies of PHNVDs in the plateau area of China are still insufficient. In China, Tibetan people are the largest population living in the plateau area, estimated at 7.8 million, and the majority inhabits the Southwestern Himalayan Plateau area (mean altitude over 4500 m). Two national surveys have reported that Tibetan people had the highest incidence of stroke among the Chinese population [35,36], and unlike the stroke distribution in other populations in which the ischemic subtype accounts for the majority of cases, hemorrhagic stroke occurs in the majority (74.1%) of cases in Tibetans [3].

More interestingly, our previous study revealed that Tibetan PHNVD patients had a significantly higher risk of cerebral infarction than contemporary Han Chinese patients (the majority of the Chinese population), which is similar to other reports in the literature [34]. However, to our knowledge, no study has revealed the mechanism for this increased risk of cerebral infarction. Due to the high-altitude, low pressure and an oxygen-thin atmosphere, the serum hemoglobin (HGB) concentration of Tibetan people is increased to compensate for these factors [5,10,20,30]. Several previous studies have provided evidence for increased blood viscosity caused by the increased HGB concentration [7,16,17], and other studies have reported that high blood viscosity is positively associated with the development of cerebral infarction [6,9,14,23]. Here, we propose a hypothesis for the first time that the elevated HBG concentration is correlated with the high incidence of cerebral infarction among Tibetan PHNVD patients.

Using the database of the West China Hospital of Sichuan University

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(WCH), the largest medical center in the West China area, we performed a retrospective analysis of 284 Tibetan PHNVD patients to determine whether the HGB concentration could be considered a predictive indicator of in-hospital cerebral infarction. The results of our study will facilitate the understanding of PHNVDs in the plateau area of China.

2. Patient and methods

2.1. Study design and participants

This study was a retrospective case control study that was approved by the institutional review board (IRB) of WCH. We used the hospital information system (HIS) to obtain data on Tibetan PHNVD patients who were admitted in the Department of Neurosurgery of WCH from January 2014 to June 2016. The inclusion criteria were patients identified by the discharge diagnoses in the HIS database using the key words “Tibetan”; “aneurysmal subarachnoid hemorrhage”; “spontaneous intracerebral hemorrhage” and “arteriovenous malformation”. One neurosurgeon and one neuroradiologist confirmed the diagnoses of the selected patients. Those with severe illnesses in other systems or incomplete medical profiles were excluded.

2.2. Data collection and grouping

We used the HIS to collect all data. The medical data collected included baseline information, such as age, gender, HGB concentration on admission, history of hypertension, diabetes mellitus, hypercholesterolemia, prior hemorrhagic stroke, current smoking, current drinking and admission delay in hours; treatment information, such as surgical treatment or conservative treatment; and complications during hospitalization, such as rebleeding, cerebral infarction, hydrocephalus, seizures, pulmonary infection, gastrointestinal bleeding and length of stay (LOS). Comparisons were made between patients with cerebral infarction (case group) and those without cerebral infarction (control group).

2.3. Outcomes

The primary outcome was the incidence of cerebral infarction defined as radiographic evidence of stroke due to any cause during hospitalization. Cerebral infarction was confirmed by head Computed Tomography (CT) or diffusion-weighted magnetic resonance imaging (MRI) during hospitalization. The secondary outcomes were LOS and other complications during hospitalization, including rebleeding, hydrocephalus, seizures, pulmonary infection and gastrointestinal bleeding.

2.4. Statistical analysis

SPSS statistical software (version 22.0; SPSS Inc., Chicago, Illinois, USA) and MedCalc statistical software (version 15.2; MedCalc Software, Mariakerke, Ostend, Belgium) were used for all statistical analyses. The mean ± standard deviation (SD) was reported for quantitative data. Categorical data were expressed as frequencies and percentages. The Cox proportional hazard regression model was performed for multivariate analysis. If the OR of a test is larger than 1, it is considered as risk factor, and protective factor if the OR is less than 1. The receiver operating characteristic (ROC) curve and area under the ROC curve (AUROC) were used to evaluate the ability of HGB to predict the risk of cerebral infarction. The z statistic was used to calculate the difference in the AUROC derived from the same cases, and the cutoff value that maximized the ability of the HGB concentration to predict in-hospital infarction in Tibetan PHNVD patients was calculated. Moreover, Kaplan-Meier curves were used to show and compare the in-hospital cerebral infarction curves of elevated HGB and low-normal HGB groups divided by the cutoff value of HGB. Significance was defined as $P < 0.05$, and 95% confidence intervals (CI) were calculated for each variable.

3. Results

3.1. Patients characteristics

A total of 284 Tibetan PHNVD patients were enrolled with a mean age of 48.3 ± 14.7 years, and the participants included 110 aSAH, 122 sICH and 52 AVM patients. Males accounted for 66.9% (n = 190) of all patients, and the mean HGB concentration was 162.4 ± 14.6 (g/L). Among all patients, 53.5% (n = 152), 12% (n = 34), 15.1% (n = 43), 6.7% (n = 19) and 17.6% (n = 50) had a history of hypertension, diabetes mellitus, coronary artery disease, hemorrhagic stroke and hypercholesterolemia, respectively. At the time of onset, 34.5% (n = 98) of patients were smokers and 30.6% (n = 87) used alcohol. The mean time of admission delay was 16.9 ± 14.6 h. Regarding treatment, 62.7% (n = 178) of patients underwent a surgical approach, and the remaining patients chose a conservative method. Infarction occurred in 131 (46.1%) patients during hospitalization. Additionally, 19.4% (n = 55), 5.7% (n = 17), 17.6% (n = 50), and 3.9% (n = 11) of Tibetan PHNVD patients presented with rebleeding, hydrocephalus, pulmonary infection and seizures during hospitalization, respectively.

3.2. Univariate analysis

When divided patients into two groups based on cerebral infarction (infarction group and non-infarction group), univariate analysis showed several significant differences between two groups. Patients in cerebral infarction group got significantly higher age (55.6 ± 15.8 vs 42.0 ± 13.8, $P < 0.000$), more with hypertension (61.1% vs 47.1%, $P = 0.025$), more presented with seizures (7.6% vs 0.7%, $P = 0.006$) and higher serum hemoglobin levels (181.3 ± 15.9 vs 146.2 ± 13.6, $P < 0.000$) compared with those in non-cerebral infarction group. Two groups did not differ significantly in other baseline information ($p > 0.05$). (Table 1)

3.3. Multivariate analysis

Then we did Cox proportional hazard regression analysis (multi-

Table 1
Comparisons of variables between cerebral infarction and non-cerebral infarction groups in Tibetan PHNVDs: univariate analysis.

	Cerebral infarction group (n = 131)	Non-cerebral infarction group (n = 153)	*P* value
Mean age years (mean ± SD)	55.6 ± 15.8	42.0 ± 13.8	0.000
Gender, male, n (%)	91 (69.5)	99 (64.7)	0.470
Hypertension, n (%)	80 (61.1)	72 (47.1)	0.025
Diabetes mellitus, n (%)	14 (10.7)	20 (13.1)	0.664
Hypercholesterolemia, n (%)	26 (19.8)	24 (15.7)	0.446
Prior hemorrhagic stroke, n (%)	11 (8.4)	8 (5.2)	0.408
Prior coronary artery disease, n (%)	21 (16.0)	22 (14.4)	0.825
Platelet, ×109 (mean ± SD)	207.3 ± 76.3	216.4 ± 64.7	0.278
Current smoking, n (%)	52 (39.7)	46 (30.1)	0.115
Current drinking, n (%)	39 (29.8)	48 (31.4)	0.871
Admission delay, h (mean ± SD)	15.8 ± 12.2	17.8 ± 15.7	0.238
Treatment method, surgery, n (%)	84 (64.1)	94 (61.4)	0.731
Rebleeding, n (%)	27 (20.6)	28 (18.3%)	0.734
Hydrocephalus, n (%)	10 (7.6%)	7 (4.6%)	0.405
Pulmonary infection, n (%)	27 (20.6)	23 (15.0)	0.283
Seizures, n (%)	10 (7.6)	1 (0.7)	0.006
Hemoglobin, g/L (mean ± SD)	181.3 ± 15.9	146.2 ± 13.6	0.000

PHNVDs indicate primary hemorrhagic neurovascular diseases; SD indicates standard deviation.