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ORIGINAL WORK

Lower Serum Iron and Hemoglobin Levels are Associated with Acute Seizures in Patients with Ruptured Cerebral Aneurysms

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Abstract

Background and Objective: The aim of the study is to investigate the value of serum iron and hemoglobin levels for predicting acute seizures following aneurysmal subarachnoid hemorrhage (aSAH).

Methods: Clinical and laboratorial data from patients with ruptured intracranial aneurysms were collected in the retrospective study. Age, sex, symptom onset, history of diabetes and hypertension, history of coronary artery disease, temperature, Hunt–Hess grade, Fisher grade, aneurysm location, hemoglobin, serum potassium, sodium, calcium, phosphorus, and iron were collected. Acute seizures were determined as seizures within 1 week following aSAH. Propensity score matching (PSM) analyses were performed to correct imbalances in patient characteristics between seizure and non-seizure groups.

Results: A total of 760 patients were included. Incidence of acute seizures following aSAH was 6.4%. In the univariate analysis, significant differences were detected in age, admission Hunt–Hess grade, Fisher grade, hemoglobin, serum sodium, and serum iron between seizure and non-seizure groups. In multivariate logistic regression model, lower serum iron was considered as a risk factor for acute seizures (OR 0.182, 95% CI 0.084–0.393, $p = 0.000$), as well as lower hemoglobin (OR 0.977, 95% CI 0.962–0.993, $p = 0.004$) and higher serum sodium (OR 1.072, 95% CI 1.003–1.145, $p = 0.039$). After PSM, there were no significant differences in age, admission Hunt–Hess grade, Fisher grade, and serum sodium between seizure and non-seizure groups. The matched seizure group had lower serum iron and hemoglobin levels compared with the matched non-seizure group ($p < 0.05$). The optimal cutoff value for serum iron and hemoglobin levels as a predictor of acute seizure after aSAH was determined as 9.9 mmol/L (sensitivity was 81.63% and the specificity was 65.40%) and 119 g/L (sensitivity was 63.27% and the specificity was 70.18%), respectively.

Conclusions: Serum iron and hemoglobin levels were inversely associated with a high risk of acute seizures following aSAH.

Keywords: Hemoglobin, Iron, Epilepsy, Subarachnoid hemorrhage

Introduction

Subarachnoid hemorrhage caused by ruptured cerebral aneurysms contributes to a high risk of morbidity and mortality [1]. The incidence of acute seizures within 24 h following aneurysmal subarachnoid hemorrhage (aSAH) or rebleeding is 5–27% [2]. Acute seizures, which were determined as seizures within 1 week after aSAH, were a predictor of long-term

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epilepsy and poor outcome in 2-week survivors during follow-up [3, 4]. However, mechanisms and predictors of acute seizures following aSAH remain unclear, and the administration of prophylactic antiepileptic drugs (AEDs) is controversial. Iron played a key role in the neuronal metabolic activity, neurotransmitter function, and myelination [5, 6]. A meta-analysis indicated that iron deficiency was associated with a significantly increased risk of epilepsy [7]. Previous studies also demonstrated that iron deficiency anemia was associated with complex febrile seizure in children in a case–control study [8]. However, whether lower serum iron and hemoglobin levels contribute to acute and refractory seizures following aSAH remains unclear. Thus, the aim of our study is to investigate the value of serum iron and hemoglobin levels for predicting acute seizures following aSAH.

Methods

The study protocol was approved by the ethics committee of First Affiliated Hospital of Fujian Medical University. Acute seizures were determined as seizures within 1 week after aSAH. Acute seizures were witnessed by neurosurgeons or nurses in the hospital. Patients presenting with aSAH between October 2009 and June 2018 were collected in the study. The inclusion criteria were as follows: (1) Cerebral aneurysms were diagnosed by digital subtraction angiography and/or computerized tomography angiography; (2) subarachnoid hemorrhage was confirmed by computed tomography; (3) whether patients developed acute seizures within 1 week following aSAH; (4) antiepileptic drug (sodium valproate, 1 mg/kg/h, intravenous infusion) was routinely used; (5) laboratory tests (admission values) were collected within 72 h after hemorrhage. The exclusion criteria were as follows: (1) Patients presented with multiple intracranial aneurysms; (2) patients did not present with preoperative seizures and underwent surgical intervention (including craniotomy and endovascular techniques) within 1 week following aSAH; (3) patients did not develop acute seizures and underwent surgical intervention within 1 week after aSAH; (4) patients with pre-admission and suspicious seizures described by family members. If the patients experienced with preoperative seizures within 1 week, surgical intervention could be performed within 1 week (after seizures). However, patients who underwent surgical intervention within 1 week and did not experience acute seizures (within 1 week) were excluded. If patients experienced acute seizures, administration of AEDs would be performed. Furthermore, in patients with seizures, multiple AEDs (including sodium valproate) were kept at therapeutic levels.

Data Collection

Age, sex, symptom onset, history of diabetes and hypertension, history of coronary artery disease, temperature, Hunt–Hess grade, Fisher grade, aneurysm location, hemoglobin, serum potassium, sodium, calcium, phosphorus, and iron were collected after admission. Intraparenchymal hematoma was classified as Fisher grade 4. Aneurysm location was classified as anterior cerebral artery (ACA), anterior communicating artery (ACoA), internal carotid artery (ICA), middle cerebral artery (MCA), posterior communicating artery (PCoA), and other locations.

Statistical Analysis

All the statistical analyses were performed using SPSS, version 25.0 (IBM Corp., Armonk, NY, USA). The significant differences in continuous data were performed by Student's t test and one-way variance (ANOVA). Qualitative data were compared by a Chi-squared test (χ^2 test) or Fisher's exact test. Variables significant at $p < 0.10$ level in univariate analysis were included in multivariate logistic regression analyses. For inclusion in the multivariate model, age was dichotomized as "less than 60 years" and "more than 60 years," serum iron as "$\leq$ optimal cutoff value" and "> optimal cutoff value," Hunt–Hess grade as "low grade (Grades I–II)" and "high grade (Grades III–V)," Fisher grade as "grade (Grades 0, 1, 2)" and "high grade (Grades 3, 4, 5)," aneurysm location as "ACA, ACoA, ICA, MCA, PCoA," and "other locations." $p < 0.05$ was deemed statistically significant. A MedCalc 15.2.2 (MedCalc Software, Mariakerke, Belgium) was performed to generate the receiver operating curve (ROC) and analyze the sensitivity and specificity of serum iron and hemoglobin for acute seizures. We performed propensity score matching (PSM) analysis to remove imbalances in patient characteristics between seizure and non-seizure groups. Covariates associated with acute seizures ($p < 0.05$) between seizure group and non-seizure group were included in matching. Conditional probability was estimated with the logistic regression model. The continuous data were firstly performed by normality test. If the normality assumption does not hold, then a non-parametric test is performed for assessment of associations. Also if normality is violated, the data are expressed as medians and quartiles. The seizure and non-seizure groups were matched at a ratio of 1:1 using the nearest neighboring matching algorithm.

Results

A total of 760 patients with requisite data were included in the retrospective study. Incidence of acute seizures following aSAH was 6.4%. In the univariate analysis, significant differences were detected in age, admission

Hunt–Hess grade, Fisher grade, hemoglobin, serum sodium, and serum iron between seizure and non-seizure groups ($p < 0.05$). The mean age of patients in seizure group (49 cases) was 50.69 ± 12.72 years, which was lower than that in non-seizure group (711 cases, 54.80 ± 11.48 years, $p = 0.017$). Higher Hunt–Hess grade and Fisher grade were relevant to acute seizures. Serum hemoglobin level was 117.94 ± 21.29 g/L in seizure group, which was lower than that in non-seizure group (128.90 ± 18.21 g/L, $p = 0.000$). Serum iron level was 7.44 ± 3.29 mmol/L in seizure group, which was also lower than that in non-seizure group (13.24 ± 6.95 mmol/L, $p = 0.000$). Serum sodium level was 141.80 ± 4.46 mmol/L in seizure group, which was higher than that in non-seizure group (140.43 ± 4.26 mmol/L, $p = 0.030$). In multivariate logistic regression model, lower serum iron was considered as a risk factor for acute seizures following aSAH (OR 0.182, 95% CI 0.084–0.393, $p = 0.000$), as well as hemoglobin (OR 0.977, 95% CI 0.962–0.993, $p = 0.004$) and serum sodium (OR 1.072, 95% CI 1.003–1.145, $p = 0.039$). However, in multivariate logistic regression model, significant differences in age, Hunt–Hess grade, and Fisher grade were not detected between seizure and non-seizure groups. Because significant differences were detected in age, Hunt–Hess grade, Fisher grade, hemoglobin, serum sodium, and serum iron between seizure and non-seizure groups in the univariate analysis ($p < 0.05$), PSM was performed to correct imbalances of age, Hunt–Hess grade, Fisher grade, and serum sodium.

After PSM, there were three patients in seizure group who could not be matched. There were no significant differences in age, Hunt–Hess grade, Fisher grade, and serum sodium between groups. The matched seizure group had a lower serum iron and hemoglobin levels compared with the matched non-seizure group (7.55 ± 3.19 mmol/L vs. 12.77 ± 7.90 mmol/L, and 120.34 ± 19.37 g/L vs. 133.37 ± 18.70 g/L, respectively, $p < 0.05$, Table 1). In multivariate logistic regression model (Table 2), lower serum iron was considered as a risk factor for acute seizures (OR 0.210, 95% CI 0.077–0.570, $p = 0.002$), as well as hemoglobin (OR 0.969, 95% CI 0.944–0.994, $p = 0.016$).

The ROC curve is shown in Fig. 1. The optimal cutoff value for serum iron level as a predictor of acute seizures after aSAH was determined as 9.9 mmol/L in the ROC curve (Fig. 1a, area under curve was 0.765, sensitivity was 81.63%, and the specificity was 65.40%), while that for hemoglobin was 119 g/L (Fig. 1b, area under curve was 0.660, sensitivity was 63.27%, and the specificity was 70.18%). After PSM, the optimal cutoff value for serum iron level as a predictor of acute seizures after aSAH was determined as 10.4 mmol/L in the ROC curve (Fig. 1c, area under curve was 0.708, sensitivity was 84.78%, and the specificity was 52.17%), while that for hemoglobin was 119 g/L (Fig. 1d, area under curve was 0.681, sensitivity was 60.87%, and the specificity was 78.26%).

Discussion

Identifying patients who are at high risk of acute posthemorrhagic seizure is crucial to making a clinical decision, especially in application of AEDs. The mechanism of acute and refractory seizures following aSAH remains unclear. After PSM, there were no significant differences in age, Hunt–Hess grade, Fisher grade, and serum sodium between matched groups (Table 1). The matched seizure group had lower serum iron and hemoglobin levels compared with the matched non-seizure group (7.55 ± 3.19 mmol/L vs. 12.77 ± 7.90 mmol/L and 120.34 ± 19.37 g/L vs. 133.37 ± 18.70 g/L, respectively, $p < 0.05$, Table 1). In multivariate logistic regression model (Table 2), lower serum iron was considered as a risk factor for acute seizures (OR 0.210, 95% CI 0.077–0.570, $p = 0.002$), as well as hemoglobin (OR 0.969, 95% CI 0.944–0.994, $p = 0.016$). In this study, lower serum iron and hemoglobin levels were firstly reported to be risk factors for acute seizures following aSAH. Iron was reported to be a key role in the neuronal metabolic activity, neurotransmitter function, and myelination [6]. A meta-analysis indicated that iron deficiency was associated with a significantly increased risk of epilepsy [7]. Interestingly, a decrease of iron and hemoglobin combing with an increase of IL-6 was also detected in patients with epilepsy [9]. Previous studies also demonstrated that iron deficiency anemia was associated with complex febrile seizure in children [8]. We hypothesized that intracranial hemorrhage and subsequent inflammation induced iron disturbance and iron deficiency anemia. Subsequently, anemia, decreased serum iron, and intracranial hypertension following aSAH contributed to serious cerebral ischemia, dysfunction of neuronal metabolic activity, and neuronal damage, which induced acute seizures. Few studies focus on acute seizures following aSAH. Reported risk factors for perioperative seizures following aSAH included MCA location, rebleeding, and history of hypertension, which were balanced in the study [10, 11].

With this analysis, we aim to inform clinical prophylactic administration of multiple AEDs in patients with lower serum iron and hemoglobin. Note that a limitation of previous studies is that acute seizures are not separated. Identification of patients at high risk of acute seizures may mitigate the harm of multiple AEDs to low-risk patients [2]. In the study, the burden of lower serum iron and hemoglobin levels was associated with acute

Table 1 Characteristics of seizure and non-seizure groups after PSM

Characteristics	Seizure group (group I, $n=46$)	Non-seizure group (group II, $n=46$)	p value
Age, years	51.78 (11.56)	51.80 (12.90)	0.993
Men	16	21	0.288
Hypertension			
No	26	18	0.095
Yes	20	28	
Diabetes			
No	46	43	0.242
Yes	0	3	
Coronary artery disease			
No	46	46	NS
Yes	0	0	
Temperature, °C	36.73 (0.74)	36.76 (0.74)	0.888
Hunt–Hess grade			
Grade I	2	2	0.940
Grade II	13	14	
Grade III	13	13	
Grade IV	10	7	
Grade V	8	10	
Fisher grade			
Grade 0	4	6	0.913
Grade 1	4	2	
Grade 2	8	9	
Grade 3	20	20	
Grade 4	10	9	
Aneurysm location			
ACA	2	2	0.936
ACoA	16	20	
ICA	8	6	
MCA	9	10	
PCoA	6	4	
Others	5	4	
Hemoglobin, g/L	120.34 (19.37)	133.37 (18.70)	0.001
Serum potassium, mmol/L	3.82 (0.56)	3.71 (0.53)	0.363
Serum sodium, mmol/L	142.20 (137.70–145.10)	140.60 (138.3–143.00)	0.124
Serum calcium, mmol/L	2.16 (2.08–2.29)	2.16 (2.06–2.23)	0.516
Serum phosphorus, mmol/L	0.92 (0.26)	0.89 (0.34)	0.658
Serum iron, mmol/L	7.55 (3.19)	12.77 (7.90)	0.000

Values are mean ± SD or median (interquartile range)

ACA anterior cerebral artery; *ACoA* anterior communicating artery; *ICA* internal carotid artery; *MCA* middle cerebral artery; *NS* not significant; *PCoA* posterior communicating artery; *PSM* propensity score matching

Table 2 Independent risk factors associated with acute seizures after PSM

Parameter	OR	95% CI	p value
Hypertension	1.635	0.640–4.177	0.305
Hemoglobin	0.969	0.944–0.994	0.016
Serum iron	0.210	0.077–0.570	0.002

PSM propensity score matching

seizures following aSAH. Management of anemia and low level of serum iron should be performed.

Previous studies also demonstrated that a subarachnoid burden following aSAH might trigger acute seizure [2, 12]. Another report showed that a relatively large hematoma was a predictor of early-stage seizure after hemorrhagic stroke [13]. In the study, we found that a higher Fisher grade was associated with early epilepsy.

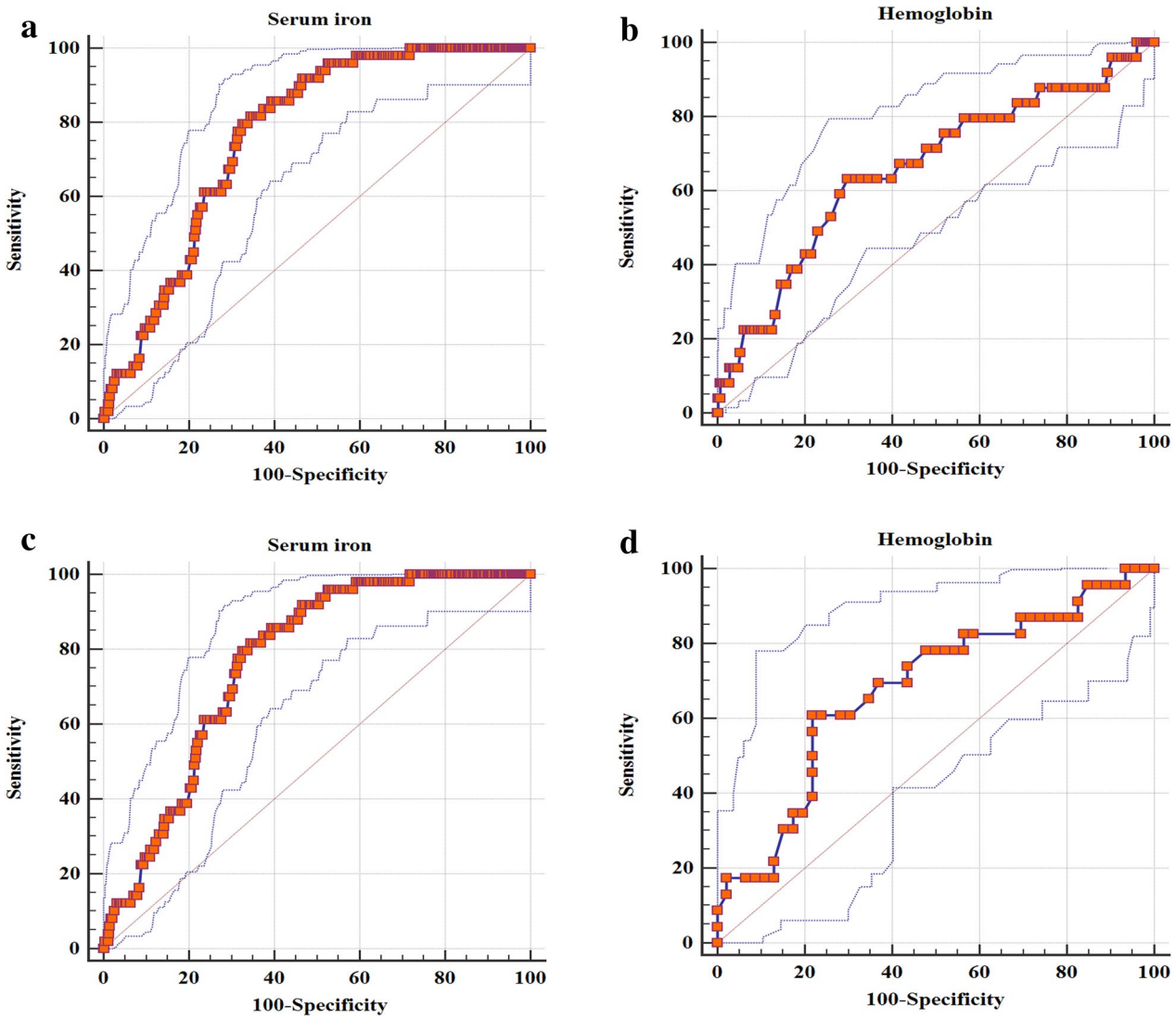

Fig. 1 ROC of hemoglobin and serum iron levels. The optimal cutoff value for serum iron level as a predictor of seizure after aSAH was determined as 9.9 mmol/L in the ROC curve (**a** area under curve was 0.765, sensitivity was 81.63%, and the specificity was 65.40%), while that for hemoglobin was 119 g/L (**b** area under curve was 0.660, sensitivity was 63.27%, and the specificity was 70.18%). After PSM, the optimal cutoff value for serum iron level as a predictor of seizure after aSAH was determined as 10.4 mmol/L in the ROC curve (**c** area under curve was 0.708, sensitivity was 84.78%, and the specificity was 52.17%), while that for hemoglobin was 119 g/L (**d** area under curve was 0.681, sensitivity was 60.87%, and the specificity was 78.26%)

Hemosiderin deposits have been considered as potential epileptogenic triggers in patients after cerebral hemorrhage [14]. Previous study also indicated that a gliotic scar, which comprised immune and glial cells, might contribute to neuronal excitability [15]. A large hematoma volume results in a large amount of hemosiderin deposits and gliotic scar. Furthermore, it has been demonstrated that early cerebral ischemia due to high intracranial pressure and spreading depolarization is a risk factor for posthemorrhagic seizures [16, 17]. One report showed that a younger age was associated with seizure after intracranial hemorrhage [13, 18]. In this study, a younger age was associated with post-hemorrhage seizure, which was consistent with several previous reports [13, 18]. Compared with the elderly, younger patients were more likely to develop large cortical infarcts and needed a higher dose of AED because of elevated drug clearance [19, 20].

In the study, patients who did not experience acute seizures (within 1 week) and underwent surgical intervention within 1 week were excluded. Lower serum iron and hemoglobin levels were considered as predictors of preoperative seizures after aSAH. However, whether

lower serum iron and hemoglobin levels could predict postoperative seizures or not remains unknown. The main limitation of this study is the relatively small sample of patients with acute seizures. Furthermore, imbalances of clinical data, including age, Hunt–Hess grade, and serum sodium, were found between two groups in the retrospective study. Because this was an exploratory and observational analysis, adjustment for multiple testing was not performed in the study. A larger sample or a randomized study is needed to verify our findings. Additionally, diagnosis of seizures was made clinically and information on electroencephalography was not obtained. Furthermore, inflammation cytokines, such as IL-6 and TNF, had not been examined.

Summary

Lower serum iron and hemoglobin levels were risk factors for acute seizures following aSAH, and management of anemia and low level of serum iron should be performed in patients with aSAH.

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Authors' Contributions
PSY designed and conducted the study protocol and reviewed the final manuscript. SFZ helped to design and conduct the study protocol and reviewed the final manuscript. ZYL corrected the manuscript, helped to analyze data and coordinated the study. PL helped to design the study protocol, to analyze data, to prepare the figures and to collect data. HCSG helped to design the study protocol and drafted the manuscript. GRC and YBZ helped to design the study protocol and to collect data. YXL and DZK coordinated the study and reviewed the manuscript.

Source of support
None.

Conflict of interest
The authors report no conflicts of interest

Ethical approval/informed consent
The study protocol was approved by the ethics committee of First Affiliated Hospital of Fujian Medical University.

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