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ORIGINAL COMMUNICATION

Cerebral infarction in acute anemia

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Abstract There are few previous studies on the relationship between cerebral infarction and acute anemia. This study presents patients with cerebral infarction in acute anemia due to marked blood loss and aims to clarify the stroke nature and possible mechanism. Patients with acute cerebral infarction and anemia following marked blood loss without systemic hypotension were recruited from 2001 to 2009. Clinical characteristics, particularly hemoglobin level, and neuroimaging findings were reviewed in detail to analyze the stroke nature and verify the possible pathogenesis. Twelve patients (males 8; mean age 74.9 years) were included. Eleven patients had cerebral infarction after acute massive gastrointestinal bleeding, and one had cerebral infarction following postoperative extensive hematoma during hospitalization. In all patients, borderzone infarction was the most characteristic finding: six had unilateral and six had bilateral borderzone infarction. Mean hemoglobin at infarction after acute blood loss was 5.8 g/dl, with 46% reduction from baseline. Of nine patients receiving detailed extracranial and intracranial vascular studies, none had severe carotid stenosis and six had intracranial stenosis. The arterial borderzones are the most vulnerable regions to a fall in cerebral perfusion. Acute anemia may produce cerebral blood flow insufficiency, reduce oxygen-carrying capacity, and result in distal-field tissue ischemic injury when hemoglobin level decreases below a critical level, especially in patients with intracranial stenosis.

Keywords Infarction · Stroke · Bleeding · Anemia

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Introduction

Cerebral infarction is considered to result from acute interruption of oxygenated blood flow. It can occur due to blockage of blood flow caused by either thrombotic or embolic occlusion, or marked focal deprivation of nutrients such as oxygen or glucose for the central nervous system. Despite numerous studies that have reported conventional risk factors [1, 2], anemia is not considered a usual vascular risk factor for cerebral infarction. Previously, several researchers have noted a link between anemia and cerebral infarction, yet this relationship was not clear and the matter was not studied adequately [3, 4].

Herein, we present a series of patients with cerebral infarction who had no systemic hypotension, but who had acute anemia following marked blood loss. Clinical and laboratory characteristics are analyzed, and pathogenesis and therapeutic aspects are discussed.

Patients and methods

We retrospectively collected data on admitted patients who had acute cerebral infarction with severe anemia following

marked blood loss at two hospitals in northern Taiwan from 2001 to 2009. The inclusion criteria were acute focal neurological deficits within 2 days after a major bleeding episode, and marked drop in hemoglobin (Hb) level (hemoglobin level <9.0 mg/dl) as compared with previous baseline at least 1 month previously, with preserved blood pressure on close monitoring during hospitalization. Patients with systemic hypotension, or cerebral infarction due to vascular malformations, dissection, cardiogenic emboli, vasculitis, radiation therapy or coagulopathy were excluded from the study.

Medical records of each patient with cerebral infarction were comprehensively reviewed in detail. Recorded data included age at diagnosis, gender, underlying systemic diseases, cerebrovascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, smoking, prior stroke history, coronary artery disease, heart disease, family history, etc.), clinical manifestations, causes of blood loss, blood pressure, laboratory findings at baseline and during acute infarction, electrocardiography and echocardiography, brain computed tomography (CT) or magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), and ultrasonographic findings.

Diagnosis of borderzone infarction (BI) was based on brain CT or MRI results. Topography of infarcts on CT scanning was assessed according to the guidelines for vascular mapping set by Damasio [5]. A BI was considered as such when the infarction area was just at the border between the two main arterial territories. Several types of BI were recognized: (1) anterior BI, i.e., infarction in the borderzone area between the superficial territory of the middle cerebral artery (MCA) and anterior cerebral artery (ACA); (2) posterior BI, i.e., infarction in the borderzone area between the superficial territory of the MCA and posterior cerebral artery (PCA); and (3) MCA internal BI, i.e., infarction in the borderzone area between the superficial and deep territory of the MCA [5–7].

Results

Twelve patients (male 8; female 4) were included. Mean age was 74.9 years (range 58–86 years). Most of the patients (90%) had several vascular risk factors, including hypertension in seven patients, diabetes mellitus in five, hyperlipidemia in four, history of prior stroke in four, cigarette smoking in two, and hypertensive heart disease in one.

When stroke symptoms developed, patients underwent brain CT scan initially. Eight patients had further brain MRI studies including diffusion-weighted imaging (DWI) to verify vascular abnormalities. In our study, neuroimaging examinations revealed that all patients had BI following acute blood loss with severe anemia. Six patients had unilateral BI presenting with acute hemiparesis, including MCA internal BI in three, anterior BI in two, and posterior BI in two. The other six patients had bilateral multiple BI presenting with coma status and bilateral limb paralysis initially. Mean age in the bilateral BI group was 78.3 years, which was slightly older than that in the unilateral group (71.5 years). Also, the Hb percentage drop was worse in the bilateral group than that in the unilateral group (54% versus 36%). Clinical, laboratory, and neuroimaging findings are summarized in Table 1. The comparison between unilateral and bilateral BI is presented in Table 2.

All patients had acute anemia due to noticeable blood loss. Ten patients were admitted due to acute upper gastrointestinal bleeding, and cerebral infarction occurred soon after hematemesis or tarry stool passage (Fig. 1a, b). Endoscopic examination was performed for each of them; gastric ulcer was found in nine patients and gastric cancer in one. Besides, one patient (case 10) was admitted for acute ischemic stroke with right hemiparesis, and aspirin was prescribed. On the fourth day of admission, this patient had acute consciousness deterioration with bilateral limbs paralysis and gaze deviation to the right. A massive amount of blood was drained from the nasogastric tube. The patient's Hb dropped from 9.2 to 4.3 g/dl. Follow-up brain MRI revealed bilateral MCA internal, and right anterior and posterior BI (Fig. 1a, b). Apart from acute upper gastrointestinal bleeding, one patient (case 9) developed acute bilateral multiple BI on the day following surgery due to postoperative bleeding with extensive hematoma at the left thigh.

In our study, these patients had marked drop in Hb level from baseline. Although their blood pressure was preserved during the course of hospitalization, with continuous intravenous fluid supply, they had acute and severe anemia when stroke symptoms appeared. The mean Hb level during acute infarction was about 5.8 g/dl, and the mean percentage reduction from baseline Hb was about 46%. In addition, their anemia was normocytic and their platelet number was still within the normal limit, with mean blood platelet counts of 205,000/μl. Brain and neck MRA or carotid ultrasonography with transcranial color-coded sonography (TCD) studies were performed for nine patients. Only mild atherosclerosis (<15% stenosis) was found at the carotid arteries. None of the patients had severe carotid stenosis or occlusion, but significant intracranial artery stenosis was noted in six of them.

Discussion

In our study, the most characteristic finding in all these patients was BI. MCA internal BI was the most common type (75%), presenting in all of the bilateral BI patients and

Table 1 Clinical, hemoglobin levels, and infarct topography in 12 patients with borderzone infarction

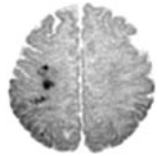
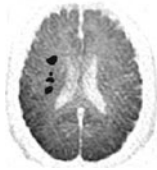
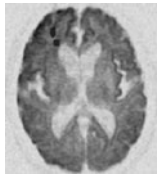
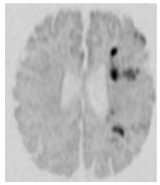
No.	Age/ sex	Risk factors	Blood pressure during stroke (mmHg)	Interval between bleeding and stroke (days)	Hemoglobin (mg/dL), baseline/stroke	MCV (μm^3)	MRA or TCD	Stroke symptoms	Location of infarction	Neuroimaging
Unilateral										
1	58/F	HTN, DM, hyperlipidemia, prior stroke	198/106	2	9.3/8.4	90	Poor window	L hemiparesis, confusion	R anterior BI	
2	69/ M	HTN, prior stroke	150/100	2	11.5/7.9	85	NA	L hemiparesis	R MCA internal BI	
3	73/F	Hyperlipidemia	120/70	2	11.7/6.0	88	Poor window	L hemiparesis, confusion	R anterior BI	
4	68/ M	–	128/70	1	9.4/5.3	88	L MCA and VA stenosis	R hemiparesis	L MCA internal BI	

Table 1 continued

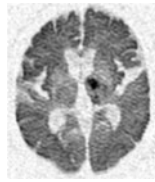
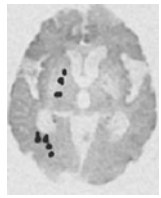
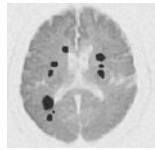
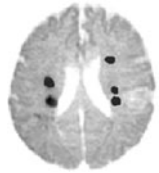
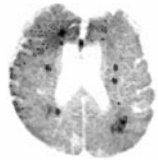
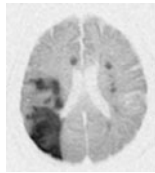
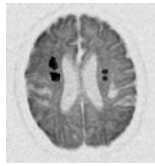
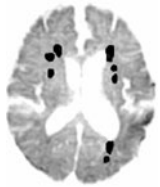
No.	Age/ sex	Risk factors	Blood pressure during stroke (mmHg)	Interval between bleeding and stroke (days)	Hemoglobin (mg/dL), baseline/stroke	MCV (μm^3)	MRA or TCD	Stroke symptoms	Location of infarction	Neuroimaging
5	75/ M	HTN, smoking, hyperlipidemia	110/69	1	12.3/6.5	84	Bilateral MCA and right VA stenosis	Slurred speech, confusion	L posterior BI	
6	86/ M	DM, hyper-homocysteinemia	142/58	2	8.0/5.1	90	Right PCA and MCA stenosis	L hemiparesis, confusion	R MCA internal and posterior BI	
Bilateral										
7	83/ M	HTN, DM, hyperlipidemia	160/80	2	11.0/3.9	87	Intracranial segmental stenosis	Bilateral paralysis, coma	Bilateral MCA internal BI and right posterior BI	
8	78/ M	HTN	140/80	1	11.7/8.8	86	Poor window	Bilateral paralysis, coma	Bilateral MCA internal BI	

Table 1 continued

No.	Age/ sex	Risk factors	Blood pressure during stroke (mmHg)	Interval between bleeding and stroke (days)	Hemoglobin (mg/dL), baseline/stroke	MCV (μm^3)	MRA or TCD	Stroke symptoms	Location of infarction	Neuroimaging
9	80/ M	HTN, smoking	150/61	2	10.2/5.6	91	Bilateral MCA and PCA stenosis	Bilateral paralysis, coma, gaze deviation to right	Bilateral MCA internal BI, anterior and posterior BI	
10	68/F	HTN, CAD	150/80	0.5	9.2/4.3	84	Bilateral MCA stenosis	Bilateral paralysis, coma, gaze deviation to right	Bilateral MCA internal BI and right posterior BI	
11	82/F	HTN, DM, prior stroke	129/51	2	12.4/3.5	84	NA	Bilateral paralysis, coma, gaze deviation to right	Bilateral MCA internal BI	
12	79/ M	DM, prior stroke	110/70	1	12.0/3.9	83	NA	Bilateral paralysis, coma	Bilateral MCA internal and left posterior BI	

BI borderzone infarction, *M* male, *F* female, *R* right, *L* left, *MRA* magnetic resonance angiography, *TCD* transcranial color-coded sonography, *HTN* hypertension, *DM* diabetes mellitus, *CAD* coronary artery disease, *NA* not applicable, *MCV* mean corpuscular volume

Table 2 Comparison between unilateral and bilateral borderzone infarction patients

	Mean age (years)	Mean risk factors	Mean drop of hemoglobin from baseline (%)
Unilateral BI	71.5	2.4	36
Bilateral BI	78.3	2.2	54

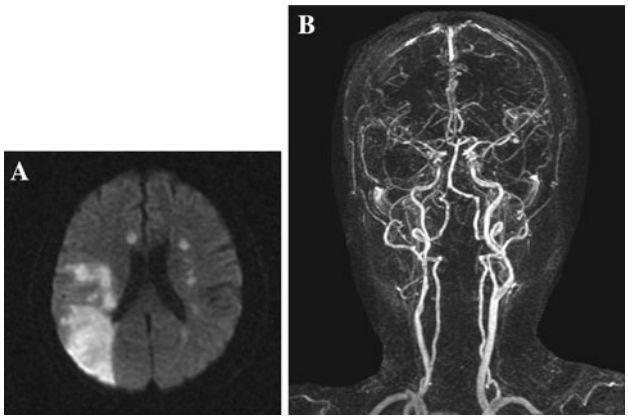


Fig. 1 Brain MRI of a 68-year-old hypertensive woman with acute consciousness disturbance, gaze deviation to the right, and bilateral limbs paralysis on the fourth day after aspirin prescription. She had marked drop of hemoglobin (9.2 to 4.3 g/dl). **a** Diffusion-weighted imaging (DWI) revealed acute bilateral MCA internal borderzone and right posterior borderzone infarcts. **b** Brain and neck MRA with contrast showed intracranial bilateral MCA and distal VA stenosis, and extracranial right internal carotid artery (ICA) mild focal stenosis

three of the unilateral BI patients. The bilateral BI group usually had more severe clinical symptoms and Hb drop as compared with the unilateral group. This implies that stroke severity may be related to blood loss course, speed, and amount.

BI is a distinctive type of stroke, also known as low-flow infarction. BI is the result of critically decreased cerebral perfusion pressure in far-downstream brain arteries that leads to severely reduced cerebral blood flow and oxygen supply in certain vulnerable brain areas [6]. Thus, borderzone areas between the major cerebral arteries are vulnerable to cerebral ischemic injury. The pathogenesis of BI is controversial. Hemodynamic and embolic factors are the suggested causes [7]. According to previous reports, bilateral BI is usually considered to occur following profound systemic hypotension due to cardiac arrest, or septic or hypovolumic shock [8, 9]. Unilateral BI is often reported to occur with ipsilateral severe carotid stenosis or occlusion [10–12]. Bogousslavsky found that BI is the most frequent type of infarction distal to an occluded internal carotid artery (ICA), and that hemodynamic disturbance was the most important factor in these patients [10]. Severe stenosis or occlusion of the carotid artery may remain asymptomatic if the collateral supply from the circle of Willis, or other extracranial to intracranial anastomoses, can adequately compensate for the reduced cerebral blood flow and cerebral perfusion pressure [13, 14]. However, if the collateral compensation is limited, this blood supply may be insufficient to meet metabolic demands.

Apart from the established causes of BI, we found that there may be another unique etiology of BI with a different pathogenesis. In our study, data on admitted patients who had acute infarction just following acute blood loss were collected, after excluding those individuals with systemic hypotension or cardiogenic emboli during the course. The most consistent neuroimaging result was BI, especially MCA internal BI. Among these patients, acute drop (mean 46%) of Hb from baseline and severe anemia (mean Hb 5.8 g/dl) during acute stroke were the characteristic findings. In addition, they usually had multiple vascular risk factors. Previous studies often revealed carotid steno-occlusion as an important pathogenesis for BI, but neither the unilateral nor bilateral BI patients in our study had severe carotid steno-occlusion. Instead, intracranial stenosis was illustrated in most of them on MRA or TCD studies. This type of BI is probably related to varied infarction mechanisms and racial differences, and may not be due to acute thrombotic occlusion or systemic hypotension. Instead, it probably results from acute anemia with severe deprivation of oxygenated blood to the distal brain field, particularly in those high-risk intracranial stenosis patients with impaired collateral circulation. Also, there is higher prevalence of intracranial stenosis with stroke in ethnic Chinese and East Asians as compared with people in Western countries [15, 16].

Previously, several researchers have noted a link among bleeding, anemia, and cerebral ischemia, but the relationship among them was unclear and the matter was not studied adequately. Decades ago, transient ischemic attacks were reported occasionally in patients with severe anemia whenever their Hb level fell below a critical level of 5–6 g/dl, and symptoms resolved with correction of the severe anemia [17–19]. Hannah and Goldberg described ten patients with cerebral infarction and anemia secondary to gastrointestinal hemorrhage [3]. Recently, a case of postoperative acute anemia-induced progression of stroke was reported [4]. Kim et al. [20] also presented a series of patients with bleeding, subsequent anemia, and stroke. They considered bleeding and subsequent anemia to be a precipitant for cerebral infarction and proposed that the hemodynamic change and enhanced thrombosis were the pathogenic mechanisms. The topography of infarcts in our study is somewhat different from in their study. Several reasons may account for this. First of all, their patients were heterogeneous. Only ten patients had definite recent active bleeding (<1 week), and in the other cases, the exact

bleeding time could not be clarified. In contrast, our patient had acute focal neurological deficits within 2 days after a clear major bleeding episode. Also, baseline Hb in their patients was unknown. In our study, the Hb drop from baseline level was marked and serious (46%). Finally, six patients in Kim et al.'s study had microcytic hypochromic anemia with decreased serum iron level. They were considered as having chronic iron-deficient anemia. However, all of our patients had normocytic anemia without iron deficiency. Neuroimaging studies revealed BI in all of them. This dissimilarity is probably related to different patient selection, bleeding onset, duration, severity, and causes of anemia between our patients and theirs. These findings in our study suggest that acute and severe anemia have a huge negative impact on cerebral circulation and contribute to BI, especially in patients with multiple vascular risk factors and carotid or intracranial stenosis.

So, how does acute anemia lead to BI in these patients, particularly at subcortical borderzone areas? In positron emission tomography (PET) studies of patients with severe carotid stenosis, the anterior borderzone is the selectively vulnerable area. These studies show diminished perfusion and rising fractional extraction of oxygen in order to maintain cerebral metabolic oxygen consumption [13, 21, 22]. Another interesting PET study showed that hemodynamic disturbance caused by ipsilateral internal carotid artery occlusion might induce selective decrease of hematocrit limited to the centrum semiovale (subcortical area), which lies in the most distal field of vascular supply [23]. This selective decrease in hematocrit might lead to a reduction in oxygen delivery relative to metabolic demand and result in high incidence of subcortical infarct. Similarly, the results could apply to patients of intracranial arteriosclerosis and stenosis with impairment of vasodilatory capacity. The subcortical borderzone areas were also probably the most vulnerable area to ischemic injury during reduction of cerebral perfusion pressure [24]. Thus, when there is acute decrease in systemic Hb concentration in patients with carotid or intracranial stenosis, oxygen uptake cannot compensate adequately for increased oxygen extraction demands. Thus, the oxygen content decreased markedly in the ischemic tissue of the subcortical borderzone areas, particularly when Hb is reduced below a critical level [25]. As a result, acute anemia may promote rapid deterioration of penumbra and lead to infarction. We consider that acute anemia can induce tissue hypoxia at the most vulnerable regions and contribute to BI in our patients, especially in those intracranial stenosis patients with insufficient collateral supply.

Other causes and relationships of anemia and infarction have been proposed in previous reports [26, 27]. Akins et al. [27] reported three severe iron-deficiency anemia patients with reactive thrombocytosis. Reactive thrombocytosis was considered as a risk factor for carotid artery thrombus formation and might lead to cerebral infarction. Also, some patients in Kim's study were found to have thrombocytosis, especially those patients with chronic iron-deficiency anemia [20]. However, thrombocytosis was not present at all in any of our patients. Thus, reactive thrombocytosis was not a possible contributing factor to BI in our patients.

With regard to treatment, urgent blood transfusion and rapid correction of the underlying cause of acute bleeding are the most important mandatory strategies for those BI patients with acute and severe anemia, not thrombolytic therapy. Time is vital for resuscitation. Ischemic hypoxic tissue will become irreversibly damaged and progress to infarction, depending upon the duration of injury [28]. In our study, several patients (cases 7–12) presented with poor consciousness and bilateral limb paralysis, similar to the manifestations of brainstem stroke [29], yet brain MRI showed acute bilateral multiple BI. Although their symptoms were severe initially, the consciousness and neurological deficits of these patients could usually get considerable improvement after rapid transfusion. On the other hand, one of our patients remained in a stupor status with left hemiplegia due to delayed treatment of acute anemia and bleeding during hospital transfer. Admittedly, the present study has a limited number of patients with acute anemia and BI, and the preliminary results should be interpreted cautiously. Some patients may be ignored clinically, and the true incidence of this type of BI is probably underestimated. More patient collection and awareness are required to clarify the relationship between acute anemia and ischemic stroke.

Our study results show that the arterial borderzones are the most vulnerable regions to ischemic injury when suffering from a major bleeding episode leading to marked Hb drop from baseline, especially in patients with intracranial stenosis and multiple vascular risk factors. Acute anemia may produce cerebral blood flow insufficiency, decrease oxygen-carrying capacity, result in tissue hypoxia, and promote rapid deterioration of the penumbra area to infarction, particularly when the Hb level decreases below a critical level. This could be another special cause of BI, easily ignored and underestimated clinically. It is worthy of attention because early recognition, rapid transfusion, and treatment of the underlying etiology of acute anemia are crucial to recovery and prognosis of these patients.

Conflict of interest statement There is no potential conflict of interest.

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