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【 CASE REPORT 】

Multiple Cerebral Infarcts Due to Severe Anemia Preceded by Migraine-like Headache with Aura

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Abstract:

We herein report a 47-year-old woman who developed migraine-like headache with aura and subsequent multiple cerebral infarcts, likely due to severe iron deficiency anemia (IDA) from menorrhagia. The progression from IDA to ischemic stroke involves several pathophysiological mechanisms, including reduction of erythrocyte deformability, reactive thrombocytosis, and anemic hypoxia. We speculate that a microembolus first caused cortical spreading depression without infarcts and that a larger thromboembolus then caused multiple infarcts. This case highlights the transition from migraine-like headache to ischemic stroke. New-onset migraine-like headache is a warning of impending ischemic stroke, and IDA may be a potential underlying cause.

Key words: ischemic stroke, migraine with aura, iron deficiency anemia

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Introduction

Anemia is common among young women, and iron deficiency is one of the leading causes. One study identified anemia in 22.3% of Japanese women <50 years old, and 25.2% of them had severe anemia (hemoglobin concentration <10 g/dL) (1). Although an association between anemia and ischemic stroke has been reported (2-4), anemia is not well-recognized as a potential cause of stroke.

Migraine-like headache without other neurologic deficits is an atypical symptom of transient ischemic attack (TIA) (5). We herein report a rare case of multiple cerebral infarcts likely due to severe iron deficiency anemia (IDA) preceded by a migraine-like headache with aura and discuss the pathogenesis of this condition.

Case Report

Two days before admission to our hospital, a 47-year-old woman developed a sudden onset of right visual field disturbance characterized by scotomas that slowly enlarged from the right side of her bilateral visual fields, accompanied by a scintillating edge. The visual disturbance lasted for approximately 15 min and then completely resolved, followed by dull pain in the bilateral forehead accompanied by nausea. The patient fell asleep during the headache and woke up without it. She subsequently experienced a similar episode the following night. Her headaches were characterized by moderate pain intensity that worsened with routine physical activity. She had no history of migraine and was not taking any medication; however, she had a three-month history of menorrhagia and fatigue.

On the day of admission, the patient developed transient right homonymous hemianopia as well as weakness and numbness in the right upper and lower limbs. A physical examination revealed conjunctival pallor, and a neurological examination revealed mild weakness in the right upper limb. Residual visual field abnormalities were not observed.

Laboratory testing revealed IDA with a hemoglobin concentration of 5.2 g/dL, mean corpuscular volume of 61.4 fL, mean corpuscular hemoglobin of 25.4 pg, and platelet count of 62.5×10^4/μL. Her serum iron concentrations was 9 μg/dL, and her ferritin concentration was 3.6 ng/dL. D-dimer (0.76

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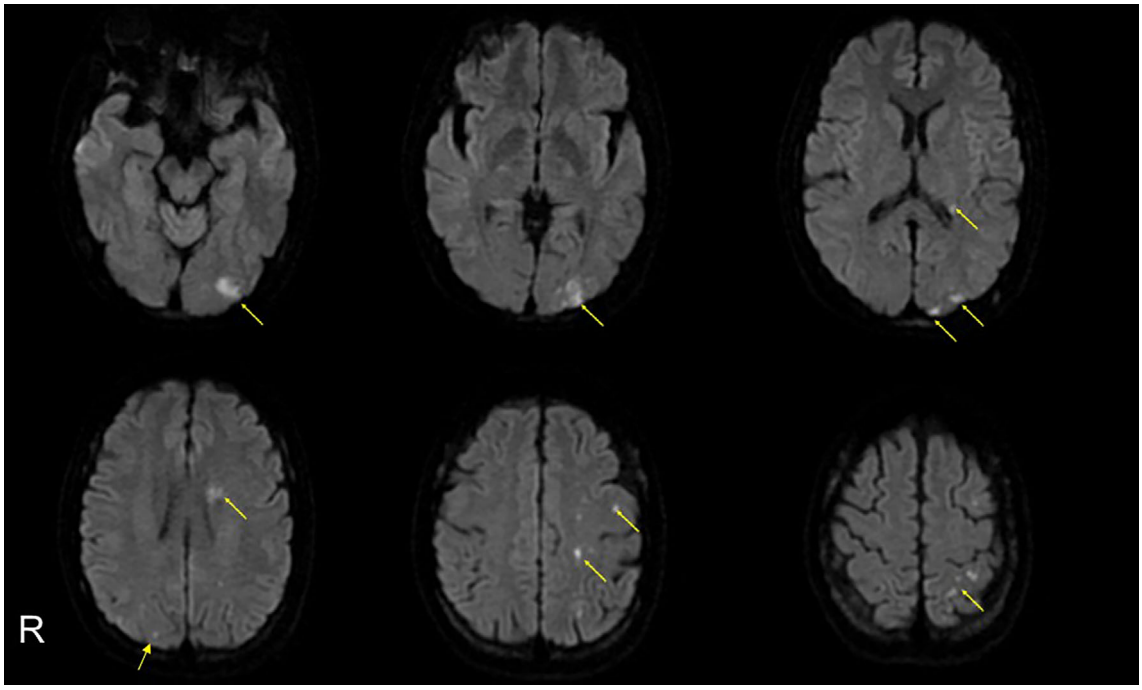

Figure 1. **Brain magnetic resonance imaging on admission shows multiple acute infarctions predominantly in the watershed area of the left hemisphere (arrows).**

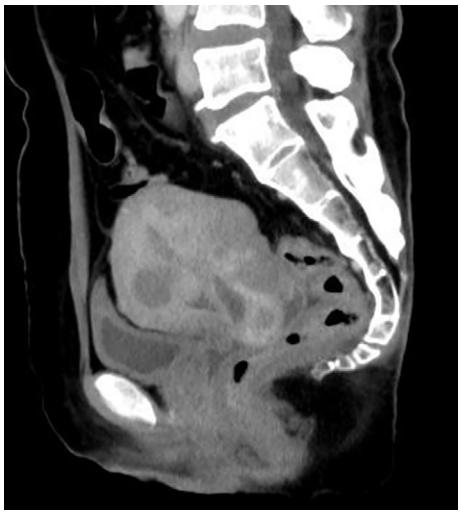

Figure 2. **Abdominopelvic computed tomography (sagittal view) revealed multiple uterine fibroids.**

μg/L) and CA-125 (22.4 U/ml) levels were within normal limits. There were no other abnormal findings in the markers of predisposing factors for thrombosis. Diffusion-weighted magnetic resonance imaging revealed multiple infarcts, predominantly in the left hemisphere (Fig. 1). Magnetic resonance angiography revealed no evidence of stenosis or occlusion of the carotid or intracranial arteries. We performed a workup for cerebral infarction and IDA. Electrocardiography, transthoracic echocardiography, and carotid Doppler ultrasonography did not reveal any embolic source. Abdominopelvic computed tomography revealed multiple uterine fibroids (Fig. 2) that were suspected to be the cause of the bleeding.

Edaravone was administered for stroke treatment, but antithrombotic agents were not used because of anemia and menorrhagia. Six units of red blood cell transfusion was administered slowly over several days to treat anemia. The patient's neurological symptoms resolved on day 5, and she was discharged from the hospital on day 9. Blood tests at the time of discharge showed improvement, with a hemoglobin concentration of 10.5 g/dL and a platelet count of 42×10^4/μL. The uterine fibroids were subsequently treated by a gynecologist, and there was no recurrence of migraine-like attacks or stroke without antiplatelet medication. We considered that a series of neurologic syndromes, beginning with migraine-like headaches, had been caused by thromboembolism due to IDA secondary to bleeding from uterine fibroids.

Discussion

This case is unique in that the initial symptom of cerebral ischemia is a migraine-like headache. The headache appeared to meet the diagnostic criteria for migraine with aura according to the International Classification of Headache Disorders, 3rd Edition (6), although no imaging studies were performed to rule out stroke. Because the patient had no history of migraine, the headache in this case was tentatively considered to be due to TIA because of recurrent, transient episodes. In previous studies, headache was analyzed in patients with TIA or stroke (7-9). The prevalence of headache at the time of these diseases ranges from 16% to 32% (7-9). In a recent study, the prevalence of *de novo* migraine-like headache at the time of TIA was 9.1% without aura and 0.8% with aura, both of which were associated with poste-

rior circulation TIA (10). At the onset of migraine-like headaches, transient ischemia would have occurred in the occipital lobe, and infarction was confirmed in this lobe.

IDA is suggested to be a potential cause of ischemic stroke (2-4). The proposed mechanisms include reduced erythrocyte deformability due to microcytosis, thrombocytosis secondary to IDA, and anemic hypoxia resulting in focal ischemia (2-4). Previous studies of cerebral infarction in patients with IDA have shown that the subcortical border zone areas are particularly susceptible to ischemia (3), as in our patient. Although uterine fibroids have previously been reported to be associated with cerebral embolism (11), we did not consider coagulation abnormalities associated with uterine fibroids because of the lack of increases in D-dimer and CA-125 levels in this case.

In the present case, it was challenging to formulate a unifying pathophysiological explanation linking migraine-like headache to subsequent ischemic stroke. Recent experimental data have indicated that focal, mild, and transient ischemia due to microemboli can trigger cortical spreading depression (CSD) without infarcts (12). Although the association between CSD and migraine headache remains unknown, CSD may contribute to the development of headache by activating perivascular trigeminal afferents (13). In the present case, the microembolus might have first caused the CSD without infarcts, and the larger thromboembolus might have subsequently caused multiple infarcts. The transition from migraine-like headache to ischemic stroke likely depends not only on the size, location, and duration of transient microthromboembolism but also on the susceptibility of the brain to the development of CSD.

The present case is interesting because it suggests a spectrum disorder involving these phenomena. It is difficult to distinguish migraine aura from TIA. In migraine, the aura is usually followed by headache, whereas in TIA, headache is less frequent (14). We therefore considered the involvement of the CSD rather than ischemia in the posterior circulation.

Reactive thrombocytosis is common in patients with IDA, and serotonin-induced platelet aggregation has been reported to be increased (15). Some data suggest that platelet-released serotonin causes migraine headache (16). Therefore, in the present case, reactive thrombocytosis might have caused the migraine-like headache. Although there are no reports of reactive thrombocytosis causing migraine-like headaches, it is a common complication in patients with myeloproliferative neoplasms, including polycythemia vera and essential thrombocythemia (17).

Several limitations associated with the present study warrant mention. First, since we did not perform a cerebral blood flow assessment using arterial spin labeling magnetic resonance imaging or single-photon emission computed tomography, the evidence for CSD is not adequate, remaining speculative. Second, we did not perform a transesophageal echocardiogram or a bubble test to detect patent foramen ovale (PFO). Although an association between migraine with aura and PFO has been implicated (18), we did not consider this involvement because of the absence of a history of migraine with aura before stroke.

In conclusion, new-onset migraine-like headache is a warning of impending ischemic stroke, and IDA may be a potential underlying cause.

The authors state that they have no Conflict of Interest (COI).

References

1. Kusumi E, Shoji M, Endou S, et al. Prevalence of anemia among healthy women in 2 metropolitan areas of Japan. Int J Hematol **84**: 217-219, 2006.
2. Akins PT, Glenn S, Nemeth PM, Derdeyn CP. Carotid artery thrombus associated with severe iron-deficiency anemia and thrombocytosis. Stroke **27**: 1002-1005, 1996.
3. Tsai CF, Yip PK, Chen CC, Yeh SJ, Chung ST, Jeng JS. Cerebral infarction in acute anemia. J Neurol **257**: 2044-2051, 2010.
4. Maguire JL, deVeber G, Parkin PC. Association between iron-deficiency anemia and stroke in young children. Pediatrics **120**: 1053-1057, 2007.
5. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. JAMA **284**: 2901-2906, 2000.
6. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. Cephalalgia **38**: 1-211, 2018.
7. Koudstaal PJ, van Gijn J, Kappelle LJ. Headache in transient or permanent cerebral ischemia. Dutch TIA study group. Stroke **22**: 754-759, 1991.
8. Vestergaard K, Andersen G, Nielsen MI, Jensen TS. Headache in stroke. Stroke **24**: 1621-1624, 1993.
9. Arboix A, Massons J, Oliveres M, Arribas MP, Titus F. Headache in acute cerebrovascular disease: a prospective clinical study in 240 patients. Cephalalgia **14**: 37-40, 1994.
10. Lebedeva ER, Gurary NM, Olesen J. Headache in transient ischemic attacks. J Headache Pain **19**: 60, 2018.
11. Higuchi E, Toi S, Shirai Y, et al. Recurrent cerebral infarction due to benign uterine myoma. J Stroke Cerebrovasc Dis **28**: e1-e2, 2019.
12. Dalkara T, Nozari A, Moskowitz MA. Migraine aura pathophysiology: the role of blood vessels and microembolisation. Lancet Neurol **9**: 309-317, 2010.
13. Karatas H, Erdener SE, Gursoy-Ozdemir Y, et al. Spreading depression triggers headache by activating neuronal Panx1 channels. Science **339**: 1092-1095, 2013.
14. Kallela M, Lindsberg PJ. How do I distinguish migraine aura from TIA attack? Duodecim **128**: 971-977, 2012.
15. Shovlin CL, Chamali B, Santhirapala V, et al. Ischaemic strokes in patients with pulmonary arteriovenous malformations and hereditary hemorrhagic telangiectasia: associations with iron deficiency and platelets. PLoS One **9**: e88812, 2014.
16. Borgdorff P, Tangelder GJ. Migraine: possible role of shear-induced platelet aggregation with serotonin release. Headache **52**: 1298-1318, 2012.
17. Shimoyama T, Yamaguchi H, Kimura K, Suzuki F, Hayashi T, Wakita S. Clinical characteristics and management of headache in patients with myeloproliferative neoplasms. Front Neurol **13**: 1051093, 2022.
18. Kato Y, Dodick DW, Schwedt TJ. Migraine comorbidity with cardiac, cardiovascular and cerebrovascular disease. Neurol Clin Neurosci **4**: 203-208, 2016.