



Acute ischemic stroke as initial manifestation of undiagnosed iron deficiency anemia: case-report and literature review

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Abstract: Cerebrovascular disease is the second leading cause of death in the United States in adults aged 65 years and older and is most commonly caused by atherosclerosis. More so, cryptogenic strokes account for one-third of all ischemic strokes. At the same time, iron deficiency anemia is prevalent worldwide and mostly affects females of childbearing age. Here we report a case of a 42-year-old female who presented with symptoms of acute ischemic stroke and was found to have severe iron deficiency anemia. After prompt investigation of other secondary causes, it was determined that her stroke was likely secondary to her iron deficiency anemia. Upon review of the literature, a few case reports showed an association between iron deficiency anemia and strokes in the adult population, but little evidence exists supporting a direct relationship between the two entities. In this case, we aim to evaluate the complex relationship between iron deficiency anemia and stroke and to define a new potential cause of ischemic stroke, which would have been considered earlier as cryptogenic. However, further studies in the future are warranted to validate our observation.

Keywords: Cerebrovascular disease; iron deficiency anemia; cryptogenic stroke

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Introduction

An acute cerebrovascular accident (CVA) is defined as a sudden onset of a neurological deficit caused by an abrupt focal injury to the central nervous system due to a disruption in the vascular supply (1). Approximately 80 percent of strokes are due to an ischemic cerebral infarction and 20 percent are due to a brain hemorrhage (2). Despite increased global awareness of the signs and symptoms of a stroke, it remains to be the second leading cause of death with someone suffering from a stroke every 40 seconds (3,4). Furthermore, strokes account for 1 out of 20 deaths in the United States with significant morbidities and mortalities leading to 34 billion US dollars in total hospital costs (2). At the same time, anemia is the most common blood disorder and has proven to be related to cardiovascular accidents (4).

A recent epidemiological study estimated that 5.6% of the United States' population met the criteria for the diagnosis of anemia. It is a global health problem that has a prevalence of 32.9% with iron deficiency anemia (IDA) being the most common cause worldwide (5,6). In about a quarter of ischemic strokes, the cause is undetermined. This may be due to the fact that a stroke workup is incomplete or delayed, multiple factors were at play causing a stroke, or that the stroke is genuinely undetermined after a full investigation, which will then be categorized as cryptogenic. IDA is an uncommon cause of acute ischemic stroke and has been reported in only three case reports (7-10). In this case, we present a 42-year-old female who developed an acute ischemic stroke that was concluded to be most likely secondary to IDA, after all other etiologies were ruled out. Our aim in this report is to identify IDA as a potential

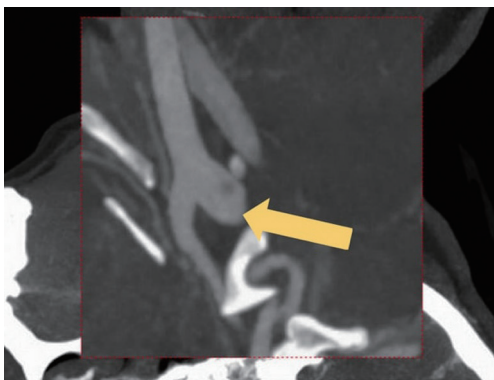


Figure 1 CTA of right internal carotid artery showing a 2.5 mm filling defect (arrow) of the right posterior wall of the internal carotid artery 5 mm from the carotid bifurcation. CTA, computed tomography angiography.

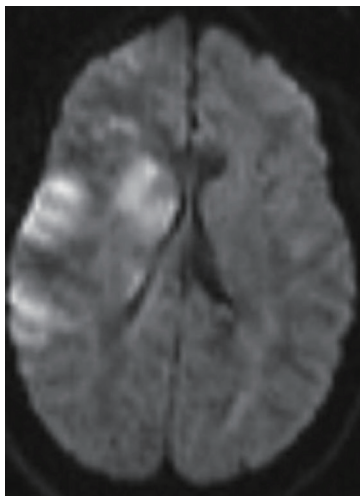


Figure 2 Diffusion weighted imaging of her brain revealing a right middle cerebral artery and anterior cerebral artery territorial infarct.

cause of ischemic strokes that could have been previously categorized as unknown etiology and thus, decrease the number of patients labeled to have cryptogenic strokes. We present the following article in accordance with the CARE reporting checklist (available at: <http://dx.doi.org/10.21037/acr-20-72>).

Case presentation

A right-handed 42-year-old previously healthy African American female presented to the emergency department

following an unwitnessed fall. Subsequently, the patient was evaluated and resuscitated in the trauma bay per Advanced Trauma Life Support protocol as a Full Activation. No other prior medical and family history was known at presentation, and the patient denied taking either blood thinners or aspirin. However, upon further investigation, she has a family history significant for hypertension and diabetes. She reported occasional alcohol use and denied substance and tobacco use. On examination, she had a National Institute of Health Stroke Scale of 13, significant for left hemisensory loss, left upper and lower extremity drift, aphasia, and left facial palsy. She had a Glasgow Coma Score of 14 with altered mental status, and bilateral rightward eye deviation. Her blood pressure was found to be elevated (200/113 mmHg), which was controlled with intravenous boluses of labetalol and intravenous nicardipine infusion with a target systolic blood pressure of 160–180. Focused Assessment with Sonography in Trauma and chest radiograph of her chest and pelvis were all negative. Electrocardiogram revealed normal sinus rhythm, and the patient received a follow-up non-contrast computed tomography (CT) of her head, which revealed no abnormalities. She had a dislocation of her left second metacarpophalangeal joint from her fall, which was surgically repaired during her hospital stay. As she presented within the stroke reperfusion window, neurology was consulted, and the patient was given tissue plasminogen activator for a suspected right middle cerebral artery syndrome. Ensuing CT angiography (CTA) of the head and neck revealed no large vessel occlusion, as noted in *Figure 1*. Furthermore, no hemodynamic stenosis of the vasculature of the neck was noted. At 24-hours, her blood pressure normalized and she was started on an oral 81 mg aspirin tablet and 80 mg of atorvastatin. Following her CTA head and neck, the patient underwent a magnetic resonance imaging (MRI) of her brain, which revealed an infarct of her right middle cerebral artery and anterior cerebral artery territories (*Figure 2*). Further investigation with a transesophageal echocardiogram revealed a normal left ventricular ejection fraction of 65% and no thrombus nor emboli. Subsequent bubble test was negative for a patent foramen ovale. The patient then received an interventional cerebral angiogram of her bilateral common and internal carotid arteries. This revealed no evidence of any filling defects of her bilateral internal carotid arteries (*Figure 3*). Subsequently, a thorough hypercoagulable work up, including antinuclear antibodies, anticardiolipin, factor VIII, antithrombin, dilute Russell's viper venom time, factor V, and Hex phospholipid neutralization, was

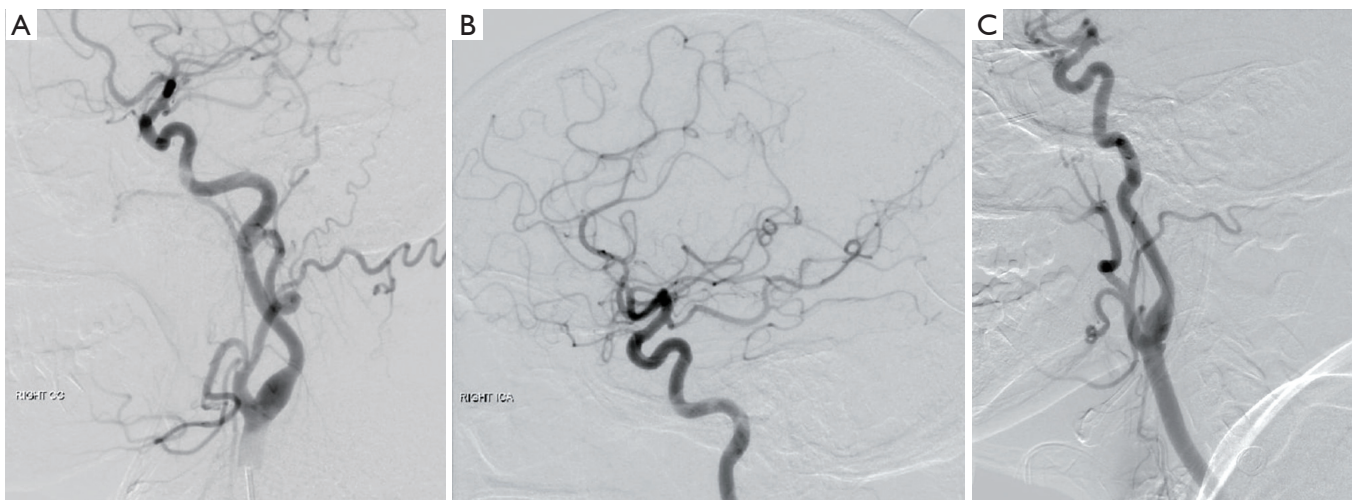


Figure 3 Interventional cerebral angiogram images. (A) Cerebral angiogram of right common carotid artery, (B) right internal carotid artery, (C) left common carotid artery showing no evidence of any filling defect in her bilateral internal carotid arteries.

Table 1 Laboratory results

Variable	Result	Normal range
White blood cell (k/ μ L)	6.6	4–12
Red blood cell (m/ μ L)	3.87	3.5–5.3
Hemoglobin (gm/dL)	7.7	12–16
Hematocrit (%)	27.3	36–48
Mean corpuscular volume (fL)	70	80–100
Mean corpuscular hemoglobin (pg)	19.9	26–34
Mean corpuscular hemoglobin concentration (gm/dL)	28.2	30–37
Red blood cell distribution width (%)	16.3	11.5–15
Platelet (k/ μ L)	407	140–440
Polychromasia	1+	–
Ovalocytes	1+	–
Schistocytes	1+	–
Microcytes	1+	–
Poikilocytes	1+	–
Anicytosis	1+	–
Hypochromasia	1+	–
Iron (μ g/dL)	16	37–170
Ferritin (ng/mL)	7	8–250
Iron saturation (%)	4	18–50
Total iron binding capacity (μ g/dL)	373	250–550

unrevealing. Furthermore, the patient’s lipid panel revealed a high-density lipoprotein of 52 mg/dL and a low-density lipoprotein of 87 mg/dL. An iron study, blood smear, and complete blood cell count revealed a microcytic, hypochromic IDA, as depicted in *Table 1*. Upon further questioning, the patient reported a history of menorrhagia. She was started on oral doses of 325 mg ferrous sulfate every other day with improvement in her symptoms. The patient was discharged home on aspirin, atorvastatin, and ferrous sulfate. On her 4-week follow up, her cardiac monitor revealed no evidence of atrial fibrillation nor abnormal heart rhythm. 6-months later, her hemoglobin normalized to 13.2 g/dL and her iron replacement therapy was discontinued.

Written informed consent was obtained from the patient for publication of this study and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Discussion

With CVA being the second leading cause of death in the United States, strokes most commonly occur in individuals 65 years and older with ischemic type accounting for the majority (1-4,11). The primary mechanism behind developing a stroke is hypoperfusion of brain tissue and decreased nutrient supply, which occurs either through an arterial blockage or systemic hypoperfusion. The later mechanism primarily manifests when the body cannot

sustain enough blood supply to maintain the brain's demand. Theoretically, anything that would affect this mechanism can result in a stroke. In the Trial of Org 10172 in Acute Stroke Treatment classification, an undetermined cause for stroke can result from one out of three possible situations: an incomplete negative investigation, more than one possible cause, or the absence of a defined cause after an extensive investigation (12). It was rarely reported that chronic anemia could result in acute ischemic stroke, especially IDA, which might have been previously classified under undetermined or cryptogenic (7-10).

The prevalence of IDA in adolescent girls and women of childbearing age ranges between 2% and 5% (13). IDA usually presents in women of childbearing age due to menstruation, which results in a slow, chronic blood loss that allows the body to adapt to low concentrations of hemoglobin. Nevertheless, when blood loss occurs acutely, it can result in a rapid decline in the blood reservoir and lead to ischemia.

While many studies investigate the role IDA serves in CVA's among the pediatric population, the relationship between the two has yet to be elucidated among the adult population. Several hypothesized pathophysiological mechanisms for IDA's role in stroke include reactive thrombocytosis, hypercoagulable state, or inadequate oxygenation to the brain from the underlying anemia (14). Subedi *et al.* reported a case of a 4-year-old child who suffered an IDA attributed ischemic stroke, in which the child's hemoglobin was 7.2 gm/dL on presentation (14). Munot *et al.* reported four cases of IDA attributed ischemic stroke, in which three of the four patients had venous sinus thrombosis (15). Also, Hartfield *et al.* reported a series of six children, who presented with an ischemic stroke or venous thrombosis after a viral prodrome, in which their findings support the evidence of a strong association between iron deficiency and ischemic events (16). Furthermore, a case-control study done in Egypt on 21 stroke cases showed that IDA was found in 57.1% of stroke cases with no identified cause, as compared to 26% of controls. They concluded that previously healthy children who developed a stroke are 3.8 times more likely to have IDA compared to healthy children who do not develop a stroke (95% CI: 1.3–11.2, $P=0.005$) (17). Moreover, in a case-control study conducted in Toronto, investigators examined 15 cases and 143 control subjects to assess the risk of strokes in patients with IDA. They discovered that IDA was significantly more common among case-patients, 8 of 15 (53%), than control subjects, 13 of 143 (9%), with a P value of <0.001 . The significance

of this study suggests that previously healthy children who suffer from strokes were 10 times more likely to have IDA than healthy children who do not suffer from a stroke (18).

Our case represents a middle-aged female who suffered an acute stroke while lacking major cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia, or substance abuse. Although the patient's blood pressure was initially elevated in the ED, all her subsequent blood pressure readings during her hospitalization were within the normal range and she did not require any blood pressure-lowering therapy. Therefore, with the absence of stroke risk factors, a normal initial laboratory stroke workup, and with the absence of atherosclerotic disease on imaging studies, this prompted us to further investigate the various causes of brain insults. The patient's low hemoglobin and ongoing severe IDA proposed the possibility of an association. We conducted a systematic review of the literature for studies published from 1960 to October 2019 in PubMed, Scopus, Web of Science, and Cochrane Central databases. The following search terms were used: "Acute Ischemic Stroke" and "Iron Deficiency Anemia." Our search was limited to individuals 18 years and older. Our search revealed a total of 8 patients (3 case-reports and 2 case series), as well as a population-based study. Our findings were similar to previous cases reported by Mehta *et al.* and Gopalratnam *et al.*, who presented two cases of female patients aged 47 and 20-year-old respectively, who developed ischemic strokes in which common secondary causes were ruled-out. Their findings lead them to conclude an association between IDA and stroke secondary to hypoxia (7,8).

On the other hand, Fluss *et al.* and another case series reported a case of a 28-year-old male and three middle-aged female patients with IDA, who suffered from ischemic strokes and carotid artery thrombi, which was attributed to reactive thrombocytosis. This finding could explain the underlying process by which IDA can result in an ischemic stroke (9,19). Moreover, in 2014, two cases were reported in Japan concerning two female patients in their 40's with IDA from chronic menorrhagia secondary to uterine fibroids who developed ischemic strokes. Their medical history was insignificant for any new neurological deficits occurring before the development of IDA or after the resolution of IDA, thus, suggesting the association between CVA secondary to IDA (10). Also, Chang *et al.* did a population base analysis in Taiwan which included 51,093 subjects. They found the adjusted odds ratio of ischemic stroke patients with prior IDA to be 1.45 (95% CI: 1.34–1.58) compared to stroke patient without IDA. Hence,

Table 2 Demographics, laboratory and Imaging findings of the previously published cases

Case	Age (years)	Gender, male/female	Hb (g/dL)	MCV (fL/cell)	Ferritin (ng/mL)	TIBC (mcg/dL)	Serum Iron (μ g/dL)	Imaging
Gopalratnam <i>et al.</i>	20	Female	5.8	64	39	481	26	MRI revealed bilateral cerebellar and left occipital lobe non-hemorrhagic infarcts. Negative brain MRA
Mehta <i>et al.</i>	47	Female	7.6	72.8	4.6	–	–	MRI of the brain showed acute infarction in right middle cerebral artery distribution. Negative MRA brain
Fluss <i>et al.</i>	28	Male	1.12	58.6	–	–	–	MRI revealed evidence of a stroke with a 4 mm lesion of the right periaqueductal gray
Akins <i>et al.</i> , patient 1	44	Female	6.6	56.6	<10	339	<10	Non-contrast head CT was normal. Cerebral arteriography demonstrated a thrombus in the bulb of the right internal carotid artery
Akins <i>et al.</i> , patient 2	20	Female	6.3	54.5	<10	355	<10	MRI of the head showed an acute right parietal infarct. Cerebral angiography revealed a right internal carotid artery thrombus
Akins <i>et al.</i> , patient 3	39	Female	7.1	62.9	<10	404	20	A bilateral carotid angiogram demonstrated a thrombus in the left common carotid artery and absent filling of the anterior division of the left middle cerebral artery
Naitu <i>et al.</i> , patient 1	42	Female	5.3	59.9	4	359	11	Brain MRI showed an acute infarction in the right cerebellar hemisphere, right frontal lobe, and left frontal lobe
Naitu <i>et al.</i> , patient 2	42	Female	11.6	69.1	3.6	400	14	Brain MRI showed a subacute infarction in the left basal ganglia and left frontal lobe. MRA and carotid artery doppler ultrasonography showed no evidence of stenosis or occlusion of the carotid or intracranial arteries

Hb, hemoglobin; MCV, mean corpuscular volume; TIBC, total iron binding capacity; RDW, red cell distribution width; MRI, magnetic resonance imaging.

they concluded a significant association between IDA and stroke (20). Further details of the previously mentioned cases' demographics, laboratory, and imaging findings are listed in *Table 2*.

Limitation

As a case report we had Lack of ability to generalize, no possibility to establish cause-effect relationship, danger of over-interpretation, publication bias, retrospective design, and distraction of reader when focusing on the unusual.

Conclusions

We believe there is an association between IDA and ischemic stroke as seen in our report. While the disease's pathophysiology remains unclear and warrants further studies, having iron studies being a part of a stroke work up, especially in young females, may prove to be beneficial. Further studies are needed to assess whether early treatment of IDA will have an impact on stroke prevalence. Our case report adds to the previous literature suggesting an association and we believe, with stronger evidence, that the

proportion of ischemic strokes classified as cryptogenic will decrease.

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Footnote

Reporting Checklist: The authors have completed the CARE guideline checklist. Available at: <http://dx.doi.org/10.21037/acr-20-72>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/acr-20-72>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this study and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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